M E M O R A N D U M

To: Timothy Leighton, EPA

From: Jonathan Cohen, ICF

Date: 20 December, 2011

Re: Contract No.: EP-W-06-091 WA 4-02:
AEATF Aerosol Study Statistical Review for HSRB

Introduction and Summary

In November 2011, AEATF submitted the final report for their study "A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting" ICF were asked to analyze the data from this study to investigate the relationship between dermal and inhalation exposures and the pesticide product usage. Note that much of the SAS code used for these analyses and some of the following description was adapted from Sarkar's SAS code (which, in turn, was based on code provided by the AHETF) and his June 2010 Statistical Review "Review of Statistical Analyses in Agricultural Handler Exposure Task Force (AHETF) Monographs."

The report describes the experimental study methodology and the measurements in detail. Briefly, three test sites in Fresno, CA, were selected to represent: cluster 1, a hotel/motel with a full kitchen; cluster 2, a hotel/motel without a food preparation area, and; cluster 3, a hotel/motel with a kitchenette. For each test site, six volunteer subjects were selected and randomly assigned different numbers of aerosol canisters containing C14 ADBAC to be sprayed from 1-1.5 canisters to 3.5-4 canisters. Each subject was given inner and outer dosimeters to wear and was also given a personal air-sampling pump attached to an OVS air sampling tube and a second personal air-sampling pump attached to a three stage Respicon™ Particle Sampler to monitor their inhalation exposure. The Particle Sampler has three filters of sizes 100 µm, 10 µm, and 2.5 µm that sample particles of sizes 10 to 100 µm, 2.5 to 10 µm, and less than 2.5 µm, respectively. Subjects were also fitted with a silicone half-mask respirator which they could volunteer to not use or use during some or all of the spraying time. Each subject then used their assigned number of aerosol canisters to spray horizontal and vertical surfaces. The percent active ingredient in the first batch of canisters used for this study was 0.126% C14 ADBAC and the percent active ingredient in the second batch of canisters was 0.104% C14 ADBAC.. Subjects were allowed to take breaks on a chair covered with plastic sheeting in a clean room, as needed. The breaks were not included in the spraying time duration but the air-sampling pumps remained on throughout the breaks. Although the study design was not a probability survey, some elements of the design used randomization. These statistical analyses treat the data as either a simple random sample or a stratified random sample, where the clusters are the strata.

The exposure measurements in the report were corrected for the average percentage recovery of field fortification samples and for the removal efficiency of hand wash (90.3%) and face and neck (89.4%) wipe samples. The face and neck wipe samples were also corrected using a half-mask respirator and safety glasses correction factor of 1.43 to account for the area of the face that was covered by the use of personal protection equipment (PPE). These analyses used the corrected measurements. The data in the report were entered and compiled into an Excel spreadsheet. This included the units conversion of the amounts of active ingredient from mg into pounds and of the mass from µg to mg.

The report data for inhalation exposure were unchanged other than the units conversions. The dermal exposure data were used to develop exposure measurements for four dermal exposure routes, as follows:

- **Long Dermal**. This case represents the dermal exposure for a subject wearing long pants and long-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Short Dermal**. This case represents the dermal exposure for a subject wearing short pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeters for the lower arm and lower leg, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Long Short Dermal**. This case represents the dermal exposure for a subject wearing long pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeter for the lower arm, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Hands Only**. This case represents the dermal exposure to the hands only and is the mass from hand wash. This case is used for comparison purposes.

The report only considered the dermal exposure for the "Long Dermal" case, and used the same definition. However for our analyses we chose a more consistent, and more conservative (i.e., more health protective) approach to deal with values reported as being below the level of quantitation (LOQ):

Several of the measured values were below the level of quantitation (LOQ). The experimental protocol also required that measurements of the inner dosimeters were not taken if the outer dosimeter was below the LOQ, although this did not in fact apply for any of the outer dosimeter measurements made in this study. As a slightly more conservative (i.e., more health protective) approach than the method used in the report, we replaced any value that was either a non-detect or was not measured by one half the LOQ. If any inner or outer dosimeter value was below the LOQ, 3 µg, each such value was replaced by 1.5 µg = 0.0015 mg. For example, if all the inner dosimeters were below the LOQ, then the total would be replaced by 0.009 mg. If the face and neck measurement was below the LOQ, 50 ng, it was replaced by 25 ng = 0.000025 mg. All the hand wash, face and neck, and outer dosimeter measurements in the study were above the LOQ. 14 of the 108 inner dosimeter measurements were below the LOQ.

For one subject (AE18, cluster 1), inner dosimeter values were much higher than all other subjects and were higher than the corresponding outer dosimeter pieces for areas of expected low exposure such as the torso. The study report suggests that this was due to significant C14 ADBAC dermal residues on the skin prior to reporting for the study, perhaps due to bathing using a product containing C14 ADBAC. No adjustments were made in these analyses for these potential outliers.

Inhalation exposure was measured using the air sampling OVS tubes and using the three filters in the Particle Sampler. The inhalation exposure concentration (mg/m^3) was calculated by dividing the corrected residue mass by the volume of air drawn. For the Particle Sampler, the report tabulated the total C14 ADBAC concentration based on summing the corrected residues on the three filters, and the percentages of the total corrected residue mass captured on each filter. The following exposure concentrations are analyzed in this memorandum:

- **Inhalation Concentration (mg/m^3).** Concentration measured by the OVS tube.

- **100µm Concentration (mg/m^3).** Total concentration measured by the Particle Sampler. This was calculated by summing the corrected residues from the three filters at Stage 1 (size 2.5µm), Stage 2 (size 10µm), and Stage 3 (size 100µm), and then dividing this total by the amount of air drawn. This measures the concentration of all particles less than 100 µm, and thus estimates the concentration of inhalable particles.

- **10µm Concentration (mg/m^3).** Concentration of particles less than 10µm measured by the Particle Sampler. This value is the sum of the corrected residues from the two filters at Stage 1 (size 2.5µm) and Stage 2 (size 10µm) divided by the amount of air drawn. This value was obtained from the study report tables by multiplying the reported 100µm concentration by the sum of the reported percentages for the Stage 1 and Stage 2 filters.

- **2.5µm Concentration (mg/m^3).** Concentration of particles less than 2.5µm measured by the Particle Sampler. This value is the corrected residue from the filter at Stage 1 (size 2.5µm) divided by the amount of air drawn. This value was obtained from the study report tables by multiplying the reported 100µm concentration by the reported percentage for the Stage 1 filter.

Note that the inhalation concentration and 100µm concentration were measured on different instruments connected to different air pumps. There were a few cases where the 100µm concentration exceeded the inhalation concentration for the same worker despite the fact that the Respicon™ Particle Sampler has an inlet that restricts particles to be less than 100 µm in size.

In the body of this memorandum we present the analysis of the unit or normalized exposure defined as the dermal or inhalation exposure divided by the pounds of active ingredient handled. Estimates of the arithmetic and geometric means and standard deviation as well as the 95th percentile are computed using the empirical data as well as two statistical models: the lognormal simple random sampling model and the lognormal mixed model. The mixed model includes the possibility of clustering due to the effects of the location. For example, the results for different subjects at the hotel/motel without a food preparation area might be correlated because of the physical similarities of the rooms, the physical similarities of the surfaces that were sprayed, the building characteristics, the investigators at that location, or other factors that are due to the selected location. The clustering includes both the random variation between locations as well as the fixed effect of the type of food preparation area (none, full kitchen, or kitchenette). Alternative statistical modeling approaches could have been used to separate out these random and fixed effects but this was not done due to the small sample size, the need to develop exposure factors applicable to all potential uses that do not depend upon the building type, and for consistency between these analyses and the previous analyses of the mop and wipe studies.

For each summary statistic we present confidence intervals. We also compute the fold relative accuracy of the summary statistics and compare with the study design benchmark of 3-fold accuracy, which was met for all 3 clothing configurations (Long Dermal, Short Dermal, Long Short Dermal) and for the total and filtered particle inhalation exposure (Inhalation, 100µm Inhalation, 10µm Inhalation, and 2.5µm Inhalation). To evaluate the statistical models we present quantile-quantile plots to compare the fit of normal and lognormal distributions to the data.

The statistical models for the normalized exposure assume that the mean value of the logarithm of the exposure is equal to an intercept plus the slope times the logarithm of the amount of active ingredient used, where the slope equals 1. To test this assumption, the regression model was fitted to the data either using simple random sampling or the mixed model and a 95% confidence interval for the slope was calculated. A statistical test was used to determine if the slope was 1 or 0, corresponding either to a valid normalized exposure model or to a case where the exposure is independent of the amount of active ingredient used. We applied this test to the three dermal exposures and to the total inhalation

exposure using the statistical mixed model. For dermal exposures it is reasonable to assume on physical grounds that the same patterns ought to apply to any type of dermal exposure, so that the slope should either be one for all types of dermal exposure or not one for all types of dermal exposure. To evaluate this issue we applied the same proportionality test to a hypothetical all dermal exposure case representing a janitor with no clothing, using a dermal exposure estimated as the sum of the exposures measured on the face and neck, hands, and all the inner and outer dosimeters. We also developed a statistical repeated measures model to analyze the three main types of dermal exposure (excluding hands only) in a single statistical model, accounting for within-worker correlations and within-location clustering. We also evaluated quadratic regression models.

The results for all the dermal and inhalation exposure routes show that the estimated intra-cluster correlation (ICC) coefficient is zero, which implies that there are no clustering and location effects, and therefore, in particular, no differences between exposures when spraying different types of food preparation areas.

The mixed model results for the four dermal exposure routes all show a positive estimated slope of at least 0.7. These dermal exposure models consistently do not reject proportionality (slope equals one) at the 5% significance level. These dermal exposure models also consistently reject independence (slope equals zero) at the 5% significance level, with the sole exception of the mixed model for hands only exposure which had a slightly negative lower confidence bound. For inhalation, the estimated slope is 0.4, but proportionality is rejected and independence is not rejected.

The appendix gives the detailed results of the corresponding analyses for dermal and inhalation exposure when the exposure is normalized by the spraying duration. The results show similar patterns to the normalization by amount of active ingredient handled but the slopes are lower, showing less support for that alternative exposure models. For inhalation, the data suggest that the exposure is either independent of spraying duration or is a non-linear function of spraying duration. A summary comparing the normalizing approaches is presented at the end of this memorandum. The mixed model analyses show that in most cases, the better of the two normalizing options considered is the amount of active ingredient handled.

The inhalation exposure measures used for the main analyses presented here are the average air concentrations (mg/m^3) over the entire period that the concentration was measured, which includes the breaks as well as the spraying durations. As an alternative approach we considered using the air C14 ADBAC mass (mg) which can be estimated as the average air concentration multiplied by the spraying duration (hours) and by an estimated 1 m^3/hour of air breathed in by someone doing light activity. These values were computed for the total inhalation mass as well as the inhalation mass for the three particle sizes. A similar statistical analysis found that the slope is significantly greater than 1. The appendix includes the detailed results for this model.

Analyses of exposure per pounds of active ingredient handled

Tables 1 and 2 summarize the normalized exposure data (per lb active ingredient handled) with the summary statistics from the 18 measurements for each dermal and inhalation exposure route, respectively.

Table 1. Summary statistics for normalized dermal exposure.*

Statistic	Normalized Long[a] Dermal (mg/lb AI)	Normalized Short[b] Dermal (mg/lb AI)	Normalized Long Short[c] Dermal (mg/lb AI)	Normalized Hands Only (mg/lb AI)
Arithmetic Mean	251.5	653.3	365.7	145.3
Arithmetic Standard Deviation	191.4	257.1	200.4	117.9
Geometric Mean	208.2	602.3	324.0	120.6
Geometric Standard Deviation	1.8	1.5	1.6	1.8
Min	88.3	248.1	142.0	54.1
5%	88.3	248.1	142.0	54.1
10%	97.5	325.2	149.5	54.4
25%	140.2	471.2	248.7	81.8
50%	193.2	648.3	325.8	121.7
75%	253.3	837.4	430.0	154.6
90%	606.0	992.3	688.2	258.6
95%	850.2	1179.2	953.4	571.2
Max	850.2	1179.2	953.4	571.2

*Using Empirical simple random sampling model
[a]Long = Long pants and long sleeves
[b]Short = Short pants and short sleeves
[c]Long Short = Long pants and short sleeves

Table 2. Summary statistics for normalized inhalation exposure.*

Statistic	Normalized Inhalation (mg/m^3/lb AI)	Normalized 100µm Inhalation (mg/m^3/lb AI)	Normalized 10µm Inhalation (mg/m^3/lb AI)	Normalized 2.5µm Inhalation (mg/m^3/lb AI)
Arithmetic Mean	59.5	47.6	25.3	11.3
Arithmetic Standard Deviation	28.1	25.0	16.1	8.5
Geometric Mean	53.3	41.9	21.3	9.1
Geometric Standard Deviation	1.6	1.7	1.8	1.9
Min	21.4	14.9	7.5	3.0
5%	21.4	14.9	7.5	3.0
10%	23.4	20.6	9.7	4.2
25%	40.8	29.2	14.4	5.2
50%	54.3	41.8	17.9	8.5
75%	82.5	54.4	30.2	14.2
90%	114.0	91.2	57.4	25.8
95%	114.2	92.1	61.0	36.8
Max	114.2	92.1	61.0	36.8

*Using Empirical simple random sampling model

The summary analyses presented in Tables 1 and 2 use the 18 measurements with a simple random sampling model that ignores the fact that the data were selected by choosing three "clusters" representing three different location types, and then measuring dermal and inhalation exposures on six subjects in each of the three clusters (a total of 18 different volunteer subjects). The six subjects in each cluster were randomly assigned six different amounts of aerosol to be sprayed, as defined by the number of canisters:

- 1 to 1.5 canisters
- 1.5 to 2 canisters
- 2 to 2.5 canisters
- 2.5 to 3 canisters
- 3 to 3.5 canisters

- 3.5 to 4 canisters

The statistical analyses use the following three alternative statistical models. Let X be the normalized exposure and X = exp(Y) so that Y = log (X), where log denotes the natural logarithm. LnGM is the log of the geometric mean. Let Z95 be the 95th percentile of a standard normal distribution, approximately 1.645.

- Empirical simple random sampling model. Code "s." Assumes that the 18 values of X were randomly drawn from an unspecified distribution. Ignores clustering. Gives empirical estimates such as in Tables 1 and 2 above.
    - Y = LnGM + Error. Error is independent and identically distributed with mean 0.
    - AMs = Arithmetic mean of X values
    - GMs = Geometric mean of X values = exp(LnGM) (= GMu)
    - GSDs = Geometric standard deviation of X values (= GSDu)
    - P95s = 95th percentile of X values
- Lognormal simple random sampling model. Code "u." Assumes that the 18 values of X were randomly drawn from a log-normal distribution. Ignores clustering.
    - Y = LnGM + Error. Error is normally distributed with mean 0, variance Vu, and standard deviation Su = √Vu.
    - AMu = Modeled arithmetic mean of X values = exp(LnGM) exp(½ Vu)
    - GMu = Modeled geometric mean of X values = exp(LnGM)
    - GSDu = Modeled geometric standard deviation of X values = exp(Su)
    - P95u = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×Su)
- Lognormal mixed model. Code "m." Assumes that three cluster effects were randomly drawn from a normal distribution and that the 18 within-cluster error terms were independently randomly drawn from another normal distribution. The error term for each subject is the sum of the cluster effect for the subject's cluster and the within-cluster error term.
    - Y = LnGM + Cluster + Error. Cluster is normally distributed with mean 0, variance Vc, and standard deviation Sc = √Vc. Error is normally distributed with mean 0, variance Vw, and standard deviation Sw = √Vw. Define V = Vc + Vw and S = √V. V is the variance of Y, and S is the standard deviation of Y.
    - ICC = Intra-cluster correlation coefficient = Vc/V.
    - AMm = Modeled arithmetic mean of X values = exp(LnGM) exp(½ V)
    - GMm = Modeled geometric mean of X values = exp(LnGM)
    - GSDm = Modeled geometric standard deviation of X values = exp(S)
    - P95m = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×S)

For the lognormal mixed model, the ICC value estimates the clustering effect and lies between 0 (no clustering) and 1 (complete clustering and negligible within-cluster variation). If ICC = 0, then the lognormal mixed model is identical to the lognormal simple random sampling model and the parameters (AM, GM, GSD, and P95) are identical for those two models.

Table 3 presents the arithmetic mean and 95th percentile estimates from the lognormal mixed model, together with 95% confidence intervals, for all the exposure routes. These are the values of AMm and P95m. The other summary statistics are presented in more detail below.

Table 3. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	**Clothing**	**Arithmetic Mean (95% confidence interval)**	**95th percentile (95% confidence interval)**
Dermal (mg/lb AI)	Long pants and long sleeves	248.1 (185.1, 338.6)	551.5 (358.5, 844.6)
	Short pants and short sleeves	660.5 (536.5, 819.6)	1221.2 (894.0, 1669.0)
	Long pants and short sleeves	366.7 (287.4, 472.4)	734.6 (511.6, 1050.9)
	Hands only	142.4 (106.7, 191.4)	311.2 (204.7, 471.2)
Inhalation (mg/m^3/lb AI)		60.3 (47.2, 77.6)	120.7 (84.1, 172.7)
100μm Inhalation (mg/m^3/lb AI)		48.1 (37.2, 63.0)	99.5 (67.9, 145.3)
10μm Inhalation (mg/m^3/lb AI)		25.5 (18.9, 35.1)	57.4 (37.0, 88.7)
2.5μm Inhalation (mg/m^3/lb AI)		11.3 (8.1, 16.1)	26.8 (16.6, 43.2)

For each exposure route, the above three statistical models were fitted to the observed data and the summary statistics listed above were calculated together with 95% confidence intervals. The 95% confidence intervals in Table 3 were computed using a parametric bootstrap. Confidence intervals computed using a non-parametric bootstrap are presented below. For these calculations, the parametric bootstrap simulations were all generated from the fitted lognormal mixed model, even for the empirical and simple random sample summary statistics, on the basis that the mixed model is the best choice for modeling the data, even if the summary statistics are developed from a simpler statistical model. For example, in Tables 1 and 2, the empirical arithmetic means are presented, which are the arithmetic means of the 18 measurements. To estimate the uncertainty of those empirical arithmetic means, data are simulated from the lognormal mixed model to calculate the parametric bootstrap confidence intervals. The arithmetic means in Table 3 are estimated using the lognormal mixed model, which is also used to estimate the confidence intervals in Table 3. The unit exposure estimates (from the lognormal mixed model) displayed in Table 3 are recommended over the empirical arithmetic means and 95th percentiles displayed in Tables 1 and 2.

The algorithm used was as follows:

Step 1:

Simulate 18 random variables Y, X from the estimated lognormal distribution superimposed upon the observed sampling structure ---;

C = LnGM + RanNor(Seed)×Sc;

Y = C + RanNor(Seed) ×Sw;

X = exp(Y);

where:

LnGM = intercept of mixed effect log-log regression model

Sc = square root of between cluster variance

Sw = square root of within cluster variance under mixed-effect model.

Step 2:

For Y:

Calculate GMs = exp(EAM)

Calculate GSDs = exp(Su)

Calculate AMu = GMs×exp(0.5×Su×Su)

Calculate P95u = GMs× exp(Z95×S)

Fit mixed lognormal model to simulated Y values

Under mixed-effects model:

Calculate GMm = exp(intercept of mixed-effects model)

Calculate GSDm = exp(square root (total variance V under mixed-effects model))

Calculate ICC = Vc /V

Calculate AMm = exp(intercept + 0.5×V)

Calculate P95m = exp(intercept + Z95×S)

where:

EAM = sample arithmetic average of Y

Su = standard deviation of Y

V = total variance under mixed-effects model

S = square root of V

Vc = between cluster variance.

For X:

Calculate arithmetic mean AMs

Calculate 95th percentile P95s

Step 3: Repeat Steps 1 and 2 10,000 times.

Steps 1 to 3 result in 10,000 values each for GSDs, GSDm, ICC, GMs, GMm, AMs, AMm, AMu, P95s, P95m, and P95u. 95% confidence intervals can be defined for each parameter by the 2.5th and 97.5th percentiles (lower and upper, respectively) of the bootstrap distribution of that corresponding parameter. Note that by definition, GSDs = GSDu and GMs = GMu. Also note that GMs = GMm for this situation because

the experiment is balanced with 3 clusters and 6 subjects in each cluster; this implies that the intercept is the same value for both the simple random sampling and mixed models.

Fold relative accuracy (*fRA*) is a measure that can be used to determine how well a statistic can describe its population parameter. Let us assume θ is a parameter and T is the sample statistic of θ (i.e., an estimate of θ). If the 2.5th and 97.5th percentiles of the sampling distribution of T can be denoted by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of sample fold relative accuracy can be theoretically calculated using the following formula provided in the AHETF Governing Document (AHETF, 2007; pg. 136):

$$fRA_{95} = \text{Max}\ (T_{97.5} / \theta, \theta / T_{2.5})$$

The actual value of θ is unknown. Thus, fRA_{95} was calculated by substituting θ with T. If the fRA_{95} of a statistic were equal to 3, then it would be correct to say: "At least 95% of the time the sample statistic will be accurate to within 3-fold of the population value". According to the AHETF Governing Document, the statistical design of the exposure monitoring study should be adequate to produce a fRA_{95} less than or equal to 3. Thus the confidence intervals calculated in the above algorithm can be used to estimate the fold relative accuracy and compare the observed fRA with the study design benchmark of 3. If the observed fold relative accuracy is greater than 3, this means that the experiment did not meet the benchmark, which would be due to differences between the distributions of the CMA data used to design the study and the experimental data collected in the study. If the fold relative accuracy benchmark is not met, then it might be desirable to collect more data for this scenario in order to meet the benchmark. Fold relative accuracy was not computed for the ICC since the estimated ICC is 0 in many cases.

The HSRB reviewers of the statistical analyses of the Mop Study ("AEATF Mop Study Statistical Review for HSRB," 19 November 2010, original version dated 28 September, 2010) suggested that a non-parametric bootstrap approach should also be considered. The non-parametric bootstrap method should be more robust since it does not assume that the fitted parametric model is the correct one. For the non-parametric bootstrap, exactly the same approach was used except that Step 1 above is replaced by the following:

Step 1:

Simulate 18 random variables Y, X by resampling at random with replacement from the original data:

> For Cluster j, the original exposure data are X(1), X(2), …, X(n_j), where n_j is the number of workers in cluster j (n_j equals 6 for the aerosol study data).
>
> Sample n_i values at random with replacement from the exposure values X(1), X(2), …, X(n_j). This gives the 6 simulated random variables X from cluster j.
>
> Repeat for all three clusters. (j = 1, 2, and 3).
>
> Y = log(X).

The Y, X values were independently resampled from the three clusters in order to preserve the covariance structure.

Tables 4 to 11 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the four dermal and four inhalation exposure routes, respectively.

Table 4. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long dermal exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.8	1.5	2.2	1.2	1.4	2.1	1.3
GSDm	1.8	1.5	2.2	1.2	1.4	2.2	1.3
ICC	0.0	0.0	0.4		0.0	0.6	
GMs	208.2	158.3	274.7	1.3	163.6	270.9	1.3
GMm	208.2	158.3	274.7	1.3	163.6	270.9	1.3
AMs	251.5	182.6	332.9	1.4	179.4	342.5	1.4
AMu	248.1	184.1	336.6	1.4	180.2	343.3	1.4
AMm	248.1	185.1	338.6	1.4	181.6	349.4	1.4
P95s	850.2	357.2	1206.3	2.4	301.1	850.2	2.8
P95u	551.5	356.5	833.0	1.5	315.3	863.3	1.7
P95m	551.5	358.5	844.6	1.5	323.0	891.3	1.7

Table 5. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized short dermal exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.5	1.3	1.8	1.2	1.4	1.7	1.1
GSDm	1.5	1.3	1.8	1.2	1.4	1.7	1.1
ICC	0.0	0.0	0.4		0.0	0.7	
GMs	602.3	492.8	737.5	1.2	504.3	722.2	1.2
GMm	602.3	492.8	737.5	1.2	504.3	722.2	1.2
AMs	653.3	532.9	812.1	1.2	546.6	767.6	1.2
AMu	660.5	536.0	816.9	1.2	549.9	776.5	1.2
AMm	660.5	536.5	819.6	1.2	556.1	777.8	1.2
P95s	1179.2	893.7	2156.7	1.8	843.7	1179.2	1.4
P95u	1220.9	888.7	1651.1	1.4	955.9	1446.4	1.3
P95m	1221.2	894.0	1669.0	1.4	982.1	1473.4	1.2

Table 6. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long short dermal exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.6	1.4	1.9	1.2	1.4	1.8	1.2
GSDm	1.6	1.4	2.0	1.2	1.4	1.9	1.2
ICC	0.0	0.0	0.4		0.0	0.6	
GMs	324.0	257.5	409.1	1.3	263.7	403.3	1.2
GMm	324.0	257.5	409.1	1.3	263.7	403.3	1.2
AMs	365.7	285.6	466.3	1.3	287.0	460.1	1.3
AMu	366.7	287.2	471.1	1.3	288.2	464.8	1.3
AMm	366.7	287.4	472.4	1.3	290.5	466.3	1.3
P95s	953.4	509.9	1417.9	1.9	442.7	953.4	2.2
P95u	734.6	509.1	1038.7	1.4	500.0	1002.4	1.5
P95m	734.6	511.6	1050.9	1.4	514.1	1016.6	1.4

Table 7. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized hands only exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.8	1.5	2.2	1.2	1.4	2.2	1.3
GSDm	1.8	1.5	2.2	1.2	1.4	2.3	1.3
ICC	0.0	0.0	0.4		0.0	0.5	
GMs	120.6	92.4	158.0	1.3	95.4	156.2	1.3
GMm	120.6	92.4	158.0	1.3	95.4	156.2	1.3
AMs	145.3	105.9	189.3	1.4	104.1	202.8	1.4
AMu	142.4	106.7	191.4	1.3	104.7	200.2	1.4
AMm	142.4	107.2	192.4	1.4	104.9	206.0	1.4
P95s	571.2	203.9	666.6	2.8	174.0	571.2	3.3
P95u	311.2	203.6	464.9	1.5	181.4	511.6	1.7
P95m	311.2	204.7	471.2	1.5	183.5	547.8	1.8

Table 8. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.6	1.4	1.9	1.2	1.4	1.8	1.2
GSDm	1.6	1.4	2.0	1.2	1.4	1.9	1.2
ICC	0.0	0.0	0.4		0.0	0.5	
GMs	53.3	42.3	67.2	1.3	43.0	65.6	1.2
GMm	53.3	42.3	67.2	1.3	43.0	65.6	1.2
AMs	59.5	46.9	76.6	1.3	47.9	72.2	1.2
AMu	60.3	47.2	77.4	1.3	48.1	73.6	1.3
AMm	60.3	47.2	77.6	1.3	48.5	73.9	1.2
P95s	114.2	83.8	233.0	2.0	83.6	114.2	1.4
P95u	120.7	83.7	170.7	1.4	87.7	153.1	1.4
P95m	120.7	84.1	172.7	1.4	89.1	157.2	1.4

Table 9. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 100μm inhalation exposure (mg/m^3/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.7	1.4	2.0	1.2	1.4	1.9	1.2
GSDm	1.7	1.4	2.0	1.2	1.4	1.9	1.2
ICC	0.0	0.0	0.4		0.0	0.5	
GMs	41.9	32.8	53.6	1.3	33.3	52.4	1.3
GMm	41.9	32.8	53.6	1.3	33.3	52.4	1.3
AMs	47.6	36.8	62.1	1.3	37.2	58.8	1.3
AMu	48.1	37.1	62.8	1.3	37.3	60.0	1.3
AMm	48.1	37.2	63.0	1.3	37.5	60.4	1.3
P95s	92.1	67.6	199.4	2.2	83.5	92.1	1.1
P95u	99.5	67.5	143.5	1.5	67.6	129.5	1.5
P95m	99.5	67.9	145.3	1.5	68.4	132.6	1.5

Table 10. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 10μm inhalation exposure (mg/m^3/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.8	1.5	2.2	1.2	1.5	2.1	1.2
GSDm	1.8	1.5	2.3	1.2	1.5	2.1	1.2
ICC	0.0	0.0	0.4		0.0	0.4	
GMs	21.3	16.1	28.2	1.3	16.4	28.0	1.3
GMm	21.3	16.1	28.2	1.3	16.4	28.0	1.3
AMs	25.3	18.7	34.5	1.4	18.8	33.1	1.3
AMu	25.5	18.8	34.9	1.4	18.7	34.0	1.4
AMm	25.5	18.9	35.1	1.4	18.8	34.1	1.4
P95s	61.0	36.9	127.6	2.1	36.4	61.0	1.7
P95u	57.4	36.8	87.5	1.6	36.0	80.9	1.6
P95m	57.4	37.0	88.7	1.6	36.4	82.2	1.6

Table 11. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 2.5μm inhalation exposure (mg/m^3/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.9	1.6	2.4	1.2	1.6	2.2	1.2
GSDm	1.9	1.6	2.4	1.3	1.6	2.3	1.2
ICC	0.0	0.0	0.4		0.0	0.4	
GMs	9.1	6.7	12.3	1.4	6.8	12.4	1.4
GMm	9.1	6.7	12.3	1.4	6.8	12.4	1.4
AMs	11.3	7.9	15.7	1.4	7.8	15.4	1.4
AMu	11.3	8.0	15.9	1.4	7.9	15.8	1.4
AMm	11.3	8.1	16.1	1.4	7.9	15.9	1.4
P95s	36.8	16.5	64.3	2.2	15.1	36.8	2.4
P95u	26.8	16.5	42.5	1.6	15.7	40.8	1.7
P95m	26.8	16.6	43.2	1.6	15.9	41.9	1.7

Tables 4 to 11 show that the ICC estimated value is zero for all the dermal and inhalation exposure routes showing that the estimated mixed and simple random sampling models are the same for those cases and that there is no variation between the different locations and types of food preparation area. All of the fold relative accuracy values met the study design benchmark of 3 except for the empirical 95th percentile for the normalized hands only exposure using the non-parametric bootstrap confidence interval. The parametric bootstrap confidence intervals were similar to the non-parametric bootstrap confidence intervals for all the dermal and inhalation exposure routes.

Quantile-quantile plots of the normalized exposure values were used to evaluate whether the data were lognormally distributed, as implied by the assumed statistical models. In each case the quantile-quantile plot compared the observed quantiles of the 18 measured values with the corresponding quantiles of a normal or lognormal distribution. A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots are presented in Figures 1 to 16. They clearly show that the lognormal distribution is a better fit than a normal distribution, and that the lognormal distribution fits reasonably well for all of the exposure routes.

Quantile plot normalized long dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled

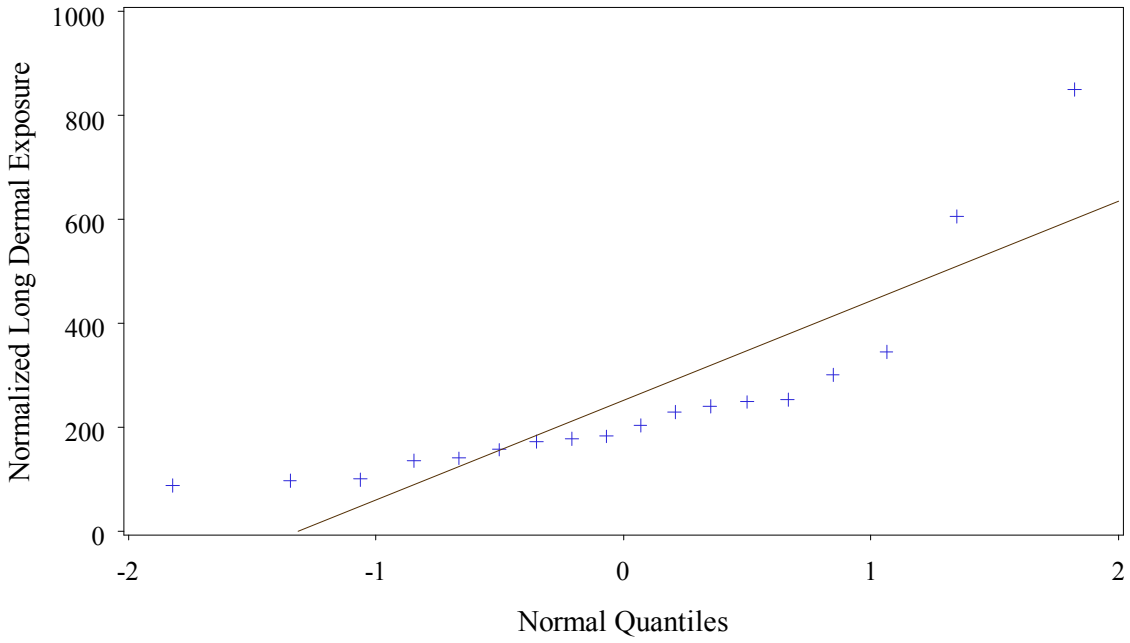

Figure 1

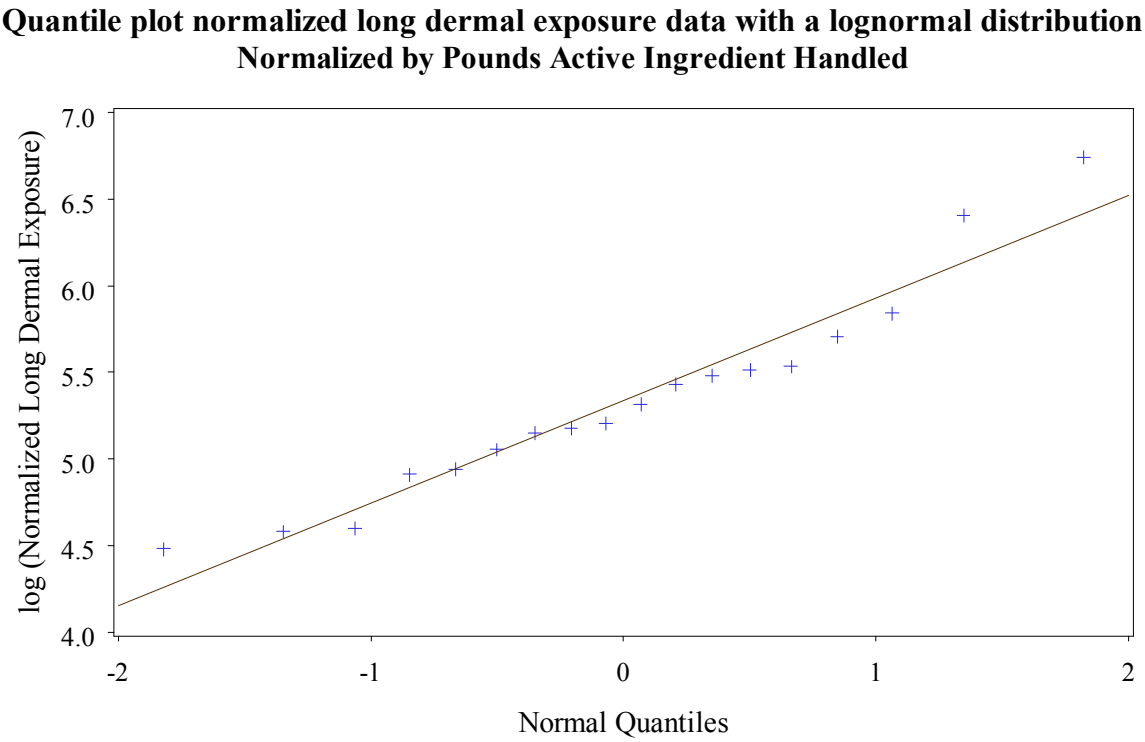
Quantile plot normalized long dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Long Dermal Exposure)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
-2
-1
0
1
2
Normal Quantiles

Figure 2

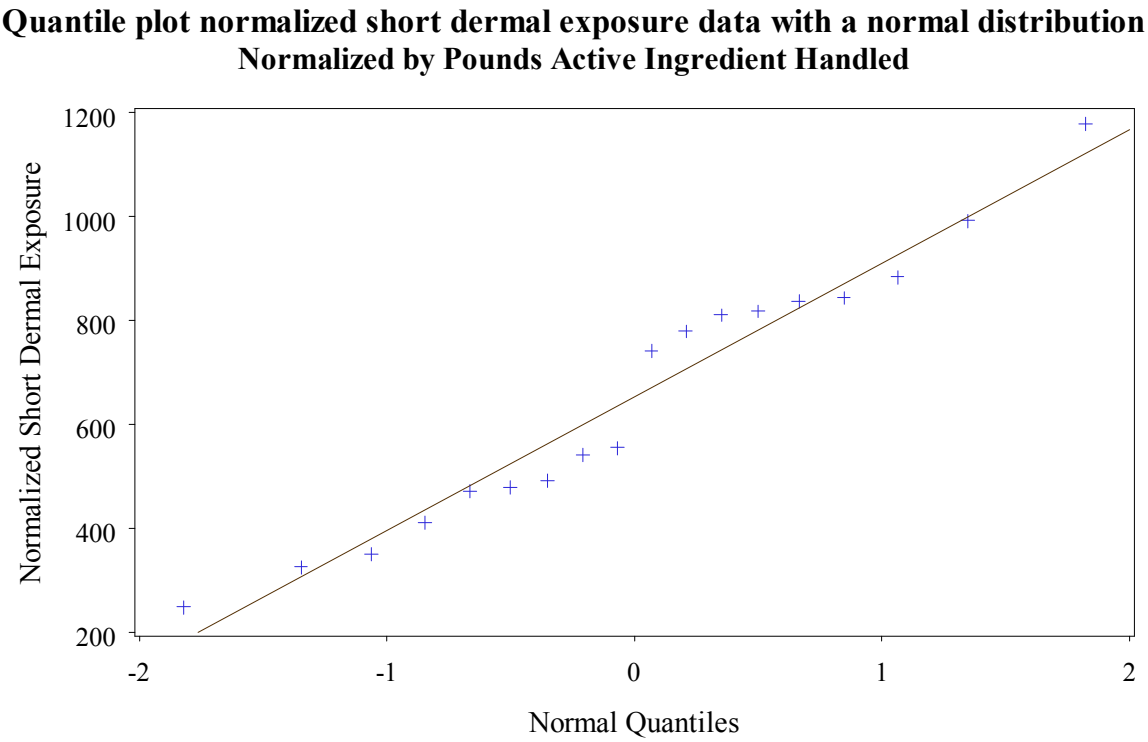
Quantile plot normalized short dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Short Dermal Exposure
1200
1000
800
600
400
200
-2
-1
0
1
2
Normal Quantiles

Figure 3

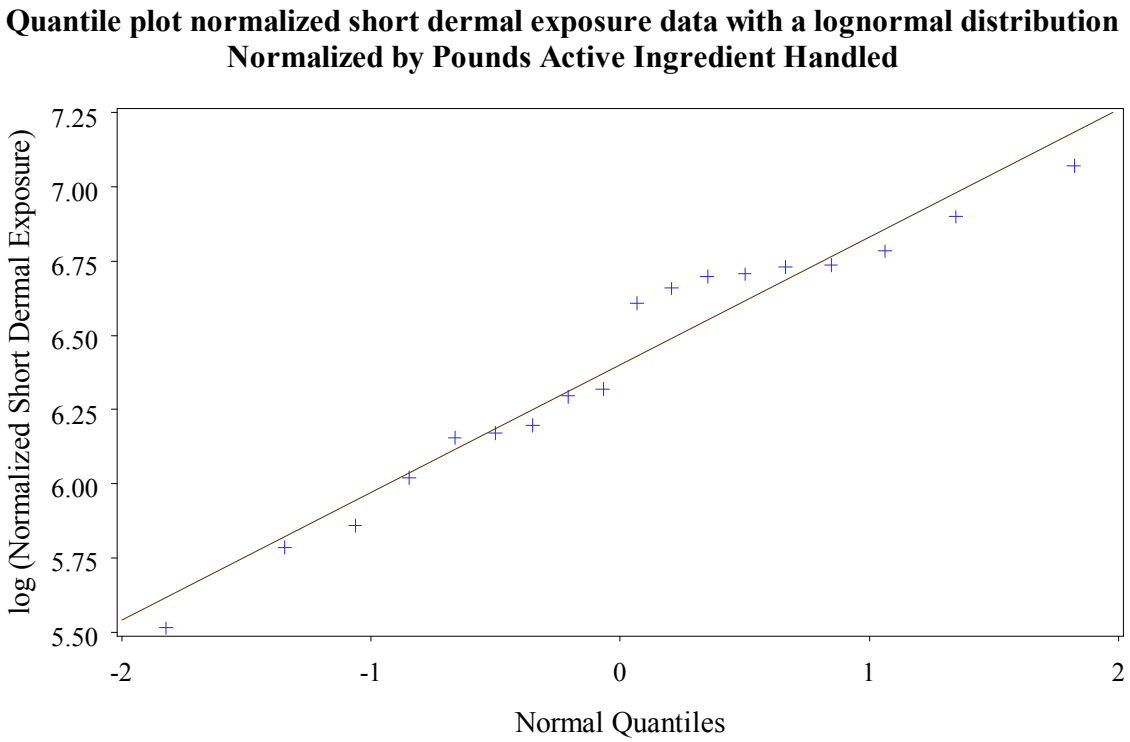
Quantile plot normalized short dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Short Dermal Exposure)
7.25
7.00
6.75
6.50
6.25
6.00
5.75
5.50
-2
-1
0
1
2
Normal Quantiles

Figure 4

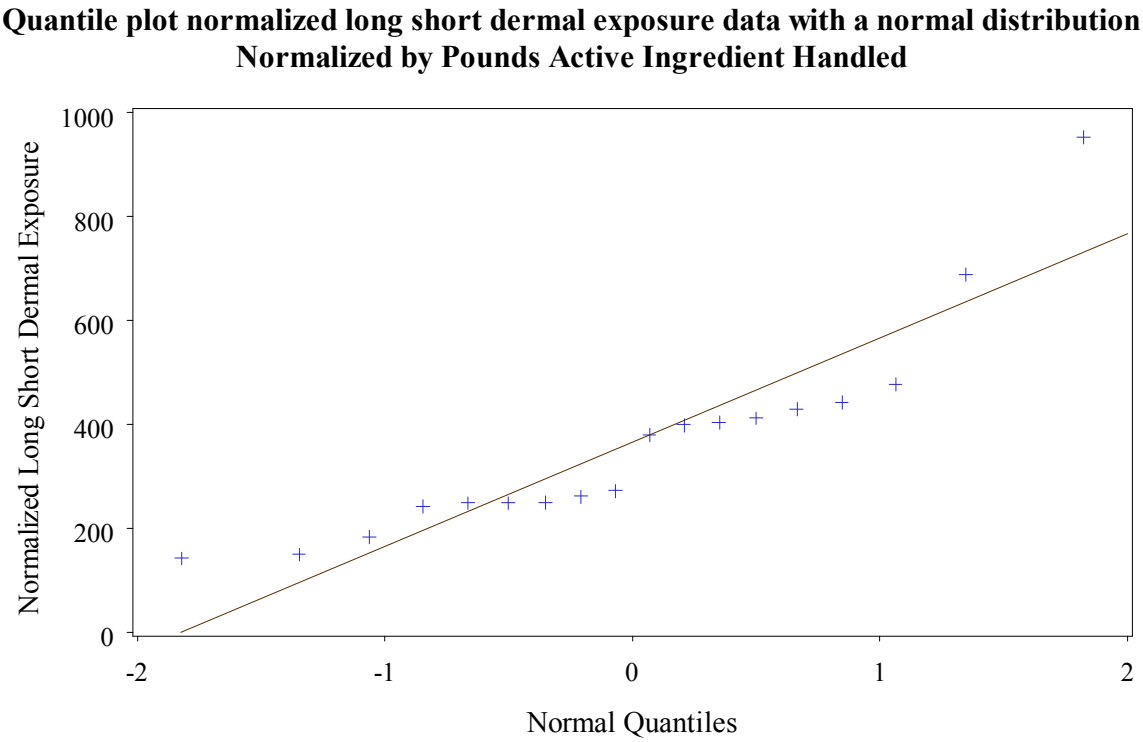
Quantile plot normalized long short dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Long Short Dermal Exposure
1000
800
600
400
200
0
-2
-1
0
1
2
Normal Quantiles

Figure 5

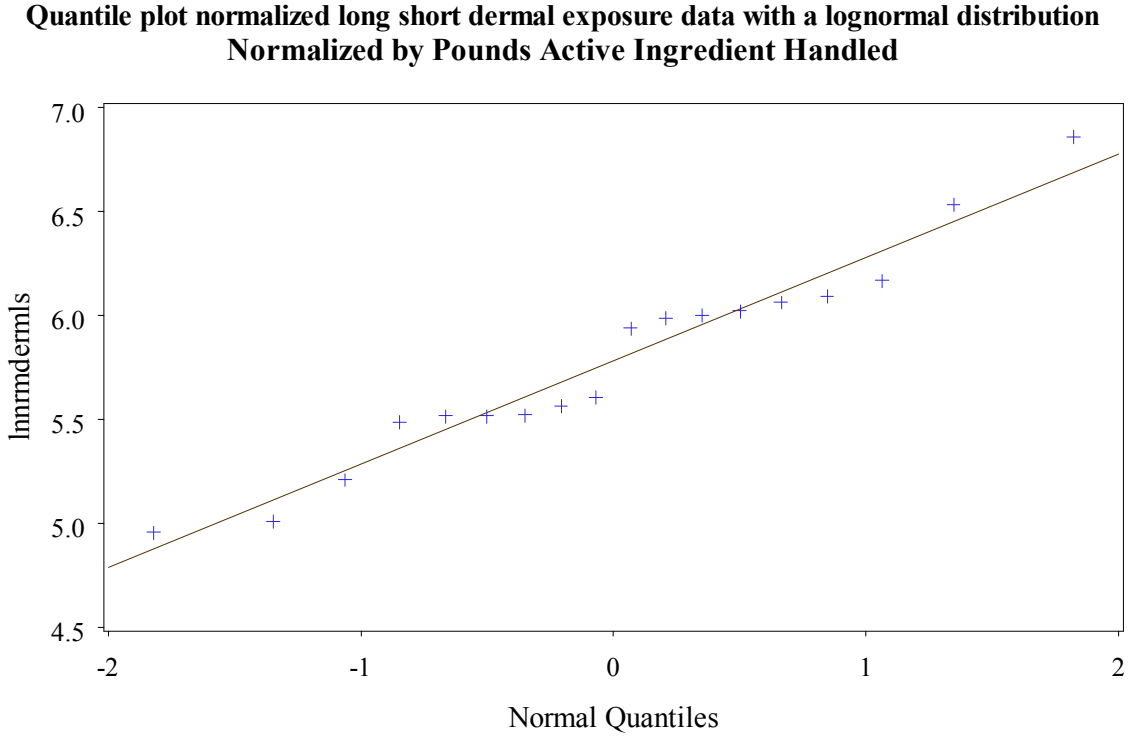
Quantile plot normalized long short dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
lnnrmdermls
7.0
6.5
6.0
5.5
5.0
4.5
-2
-1
0
1
2
Normal Quantiles

Figure 6

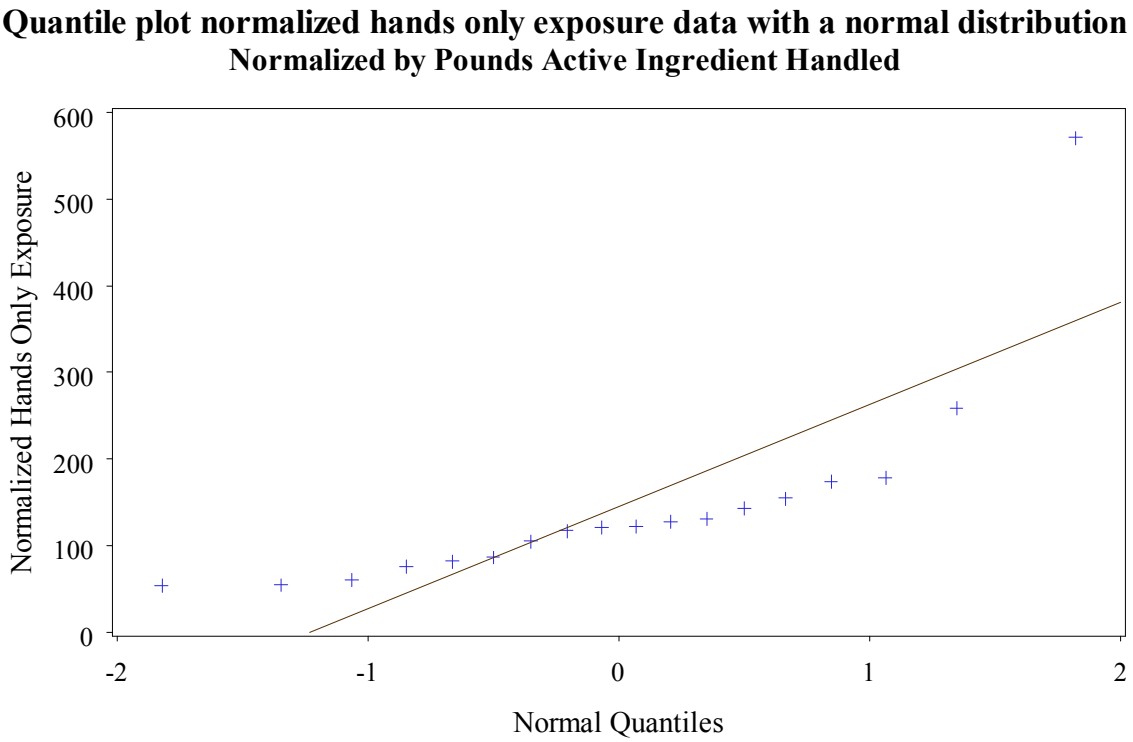
Quantile plot normalized hands only exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Hands Only Exposure
600
500
400
300
200
100
0
-2
-1
0
1
2
Normal Quantiles

Figure 7

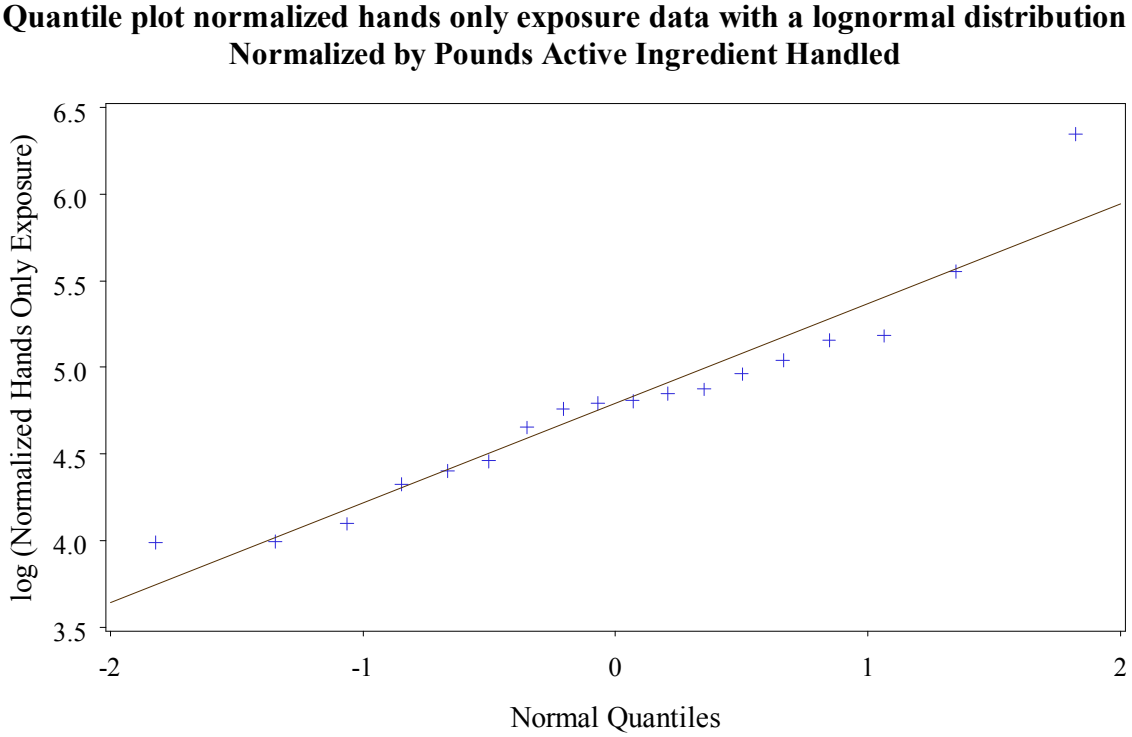
Quantile plot normalized hands only exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Hands Only Exposure)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
-2
-1
0
1
2
Normal Quantiles

Figure 8

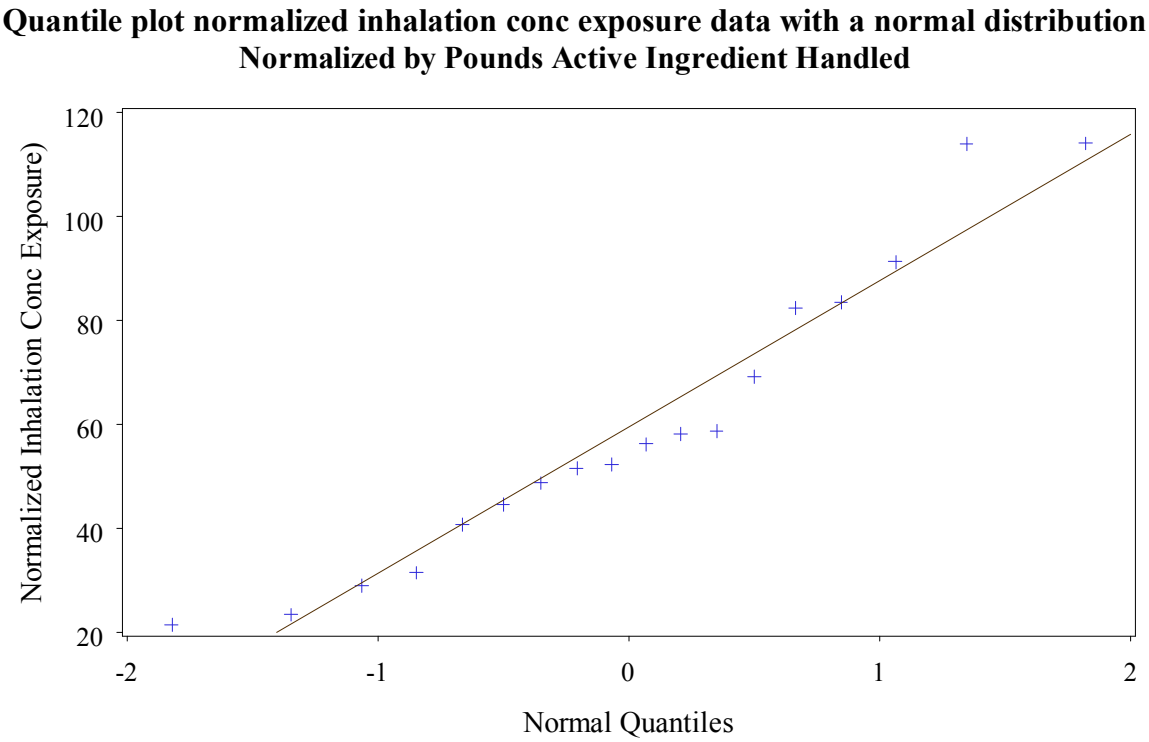
Quantile plot normalized inhalation conc exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Inhalation Conc Exposure)
120
100
80
60
40
20
-2
-1
0
1
2
Normal Quantiles

Figure 9

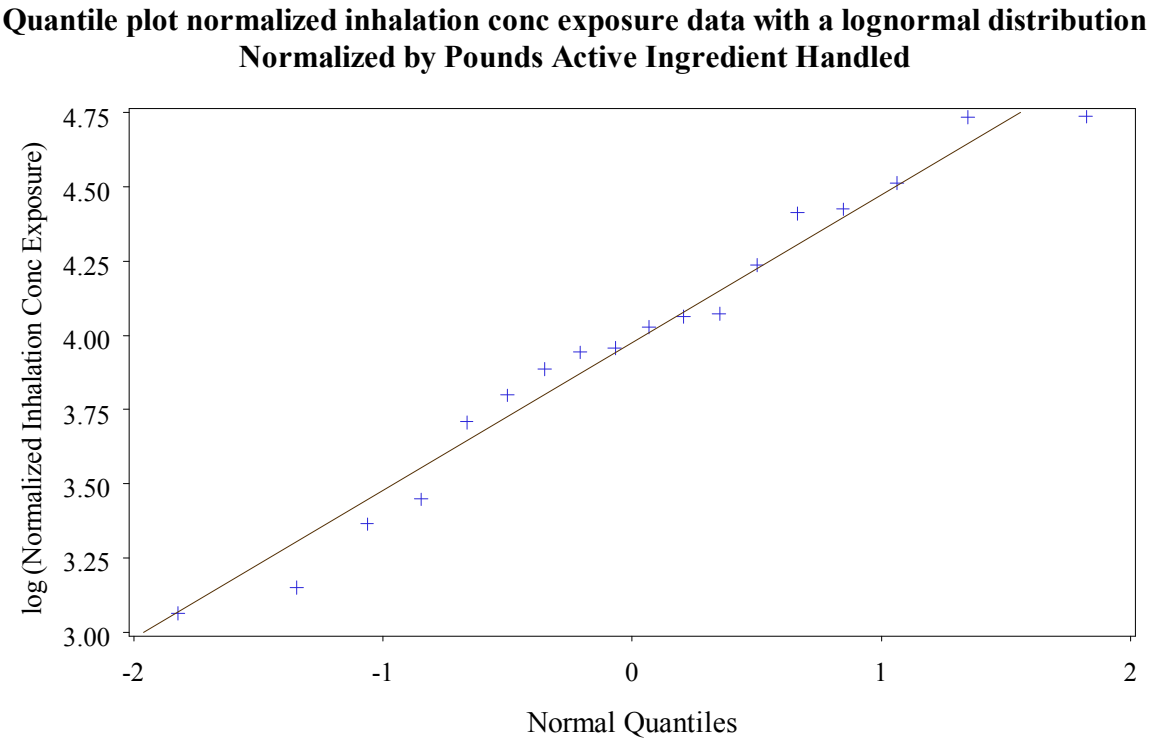
Quantile plot normalized inhalation conc exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Inhalation Conc Exposure)
4.75
4.50
4.25
4.00
3.75
3.50
3.25
3.00
-2
-1
0
1
2
Normal Quantiles

Figure 10

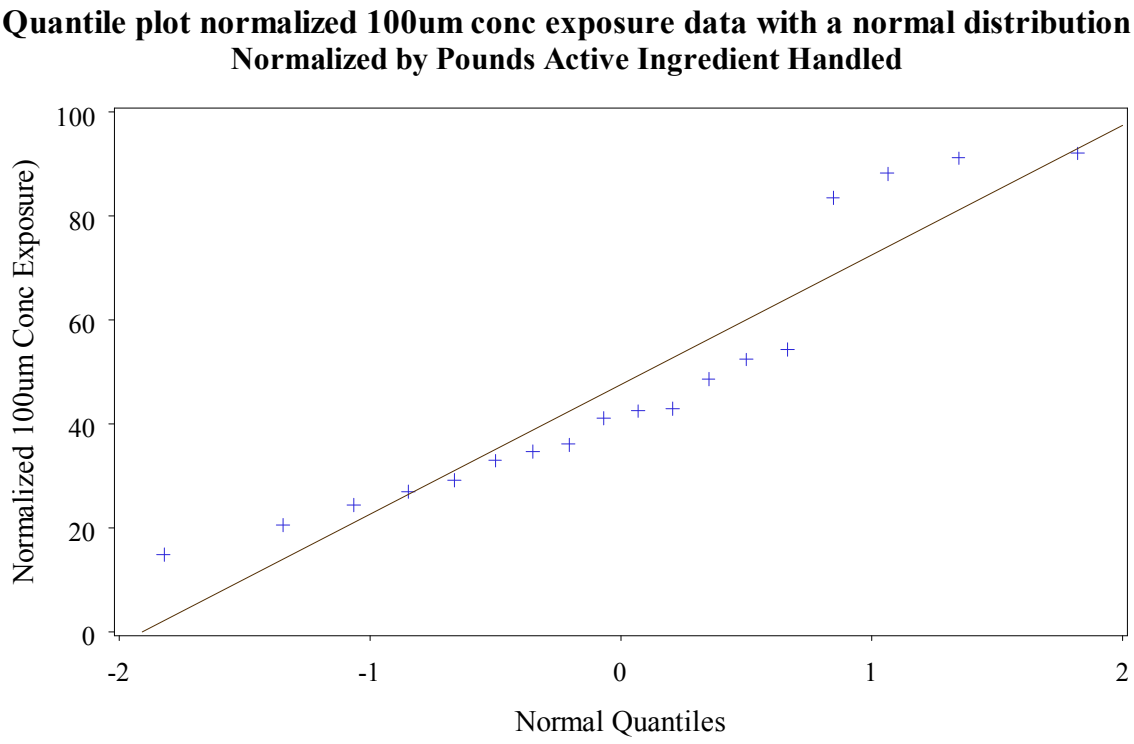
Quantile plot normalized 100um conc exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 100um Conc Exposure)
100
80
60
40
20
0
-2
-1
0
1
2
Normal Quantiles

Figure 11

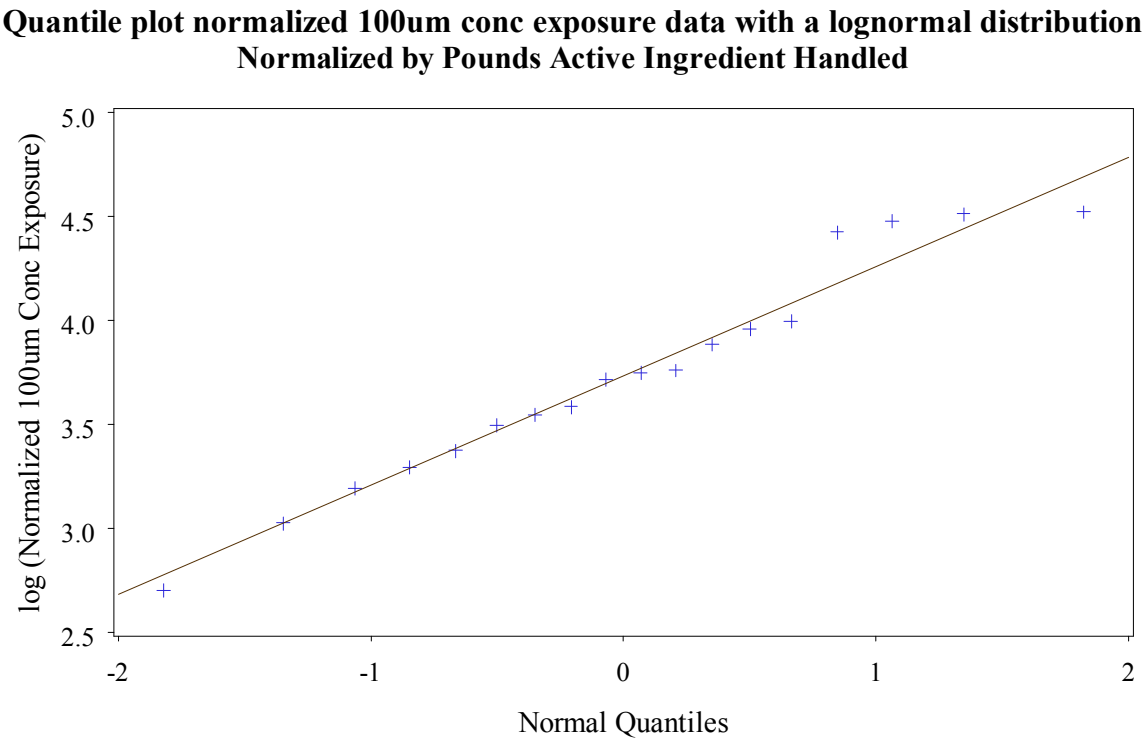
Quantile plot normalized 100um conc exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 100um Conc Exposure)
5.0
4.5
4.0
3.5
3.0
2.5
-2
-1
0
1
2
Normal Quantiles

Figure 12

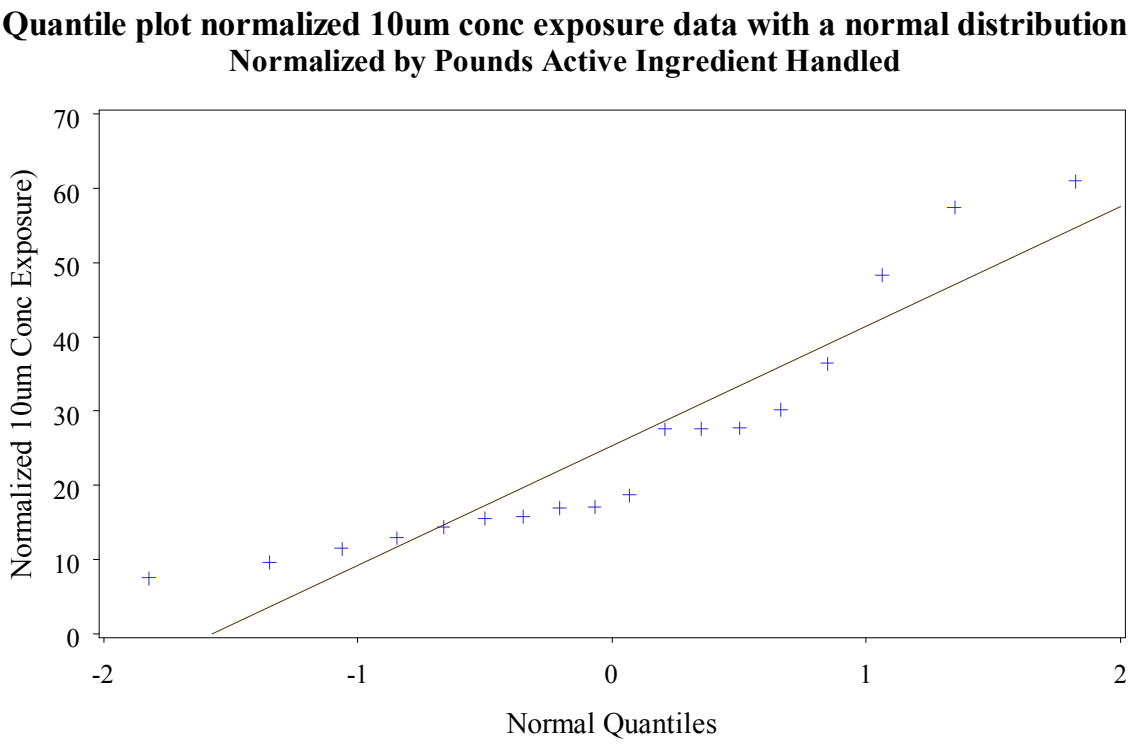
Quantile plot normalized 10um conc exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 10um Conc Exposure)
70
60
50
40
30
20
10
0
-2
-1
0
1
2
Normal Quantiles

Figure 13

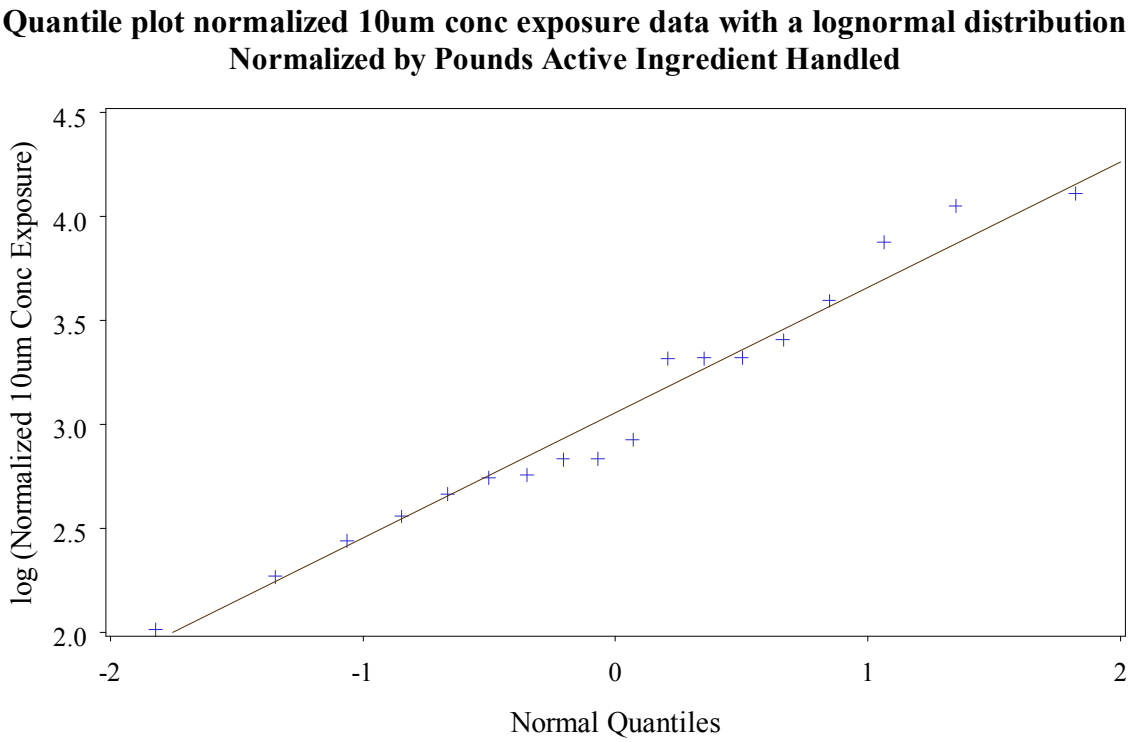
Quantile plot normalized 10um conc exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 10um Conc Exposure)
4.5
4.0
3.5
3.0
2.5
2.0
-2
-1
0
1
2
Normal Quantiles

Figure 14

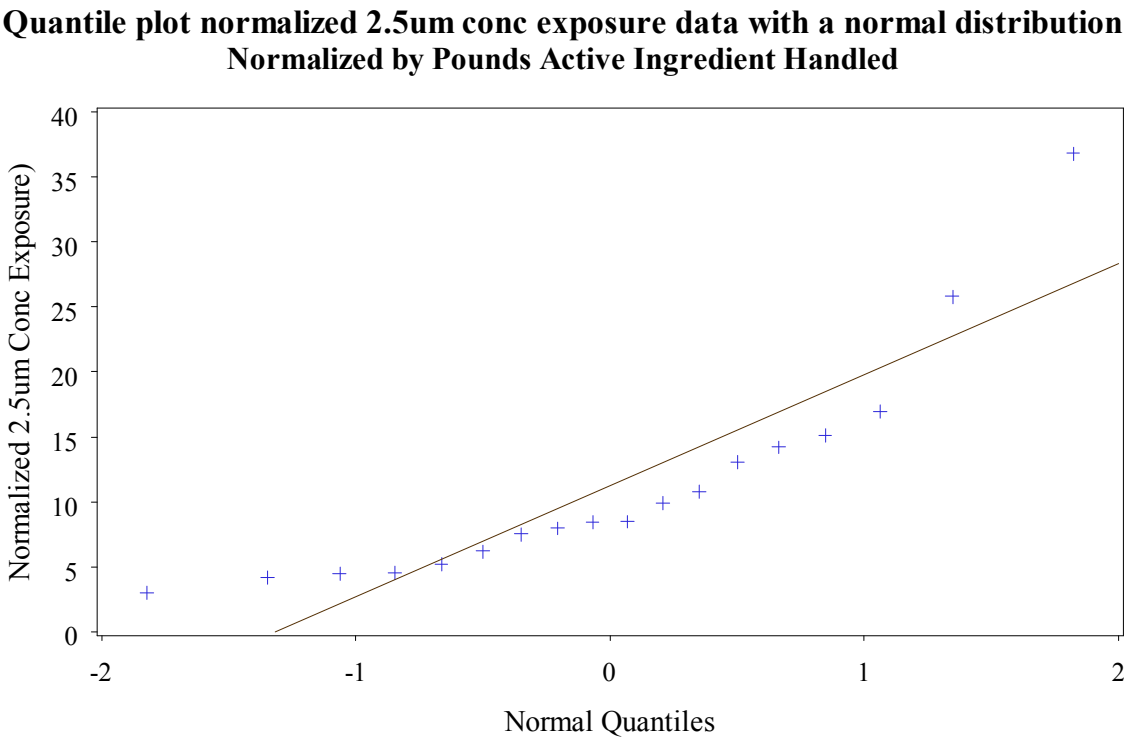
Quantile plot normalized 2.5um conc exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 2.5um Conc Exposure)
40
35
30
25
20
15
10
5
0
-2
-1
0
1
2
Normal Quantiles

Figure 15

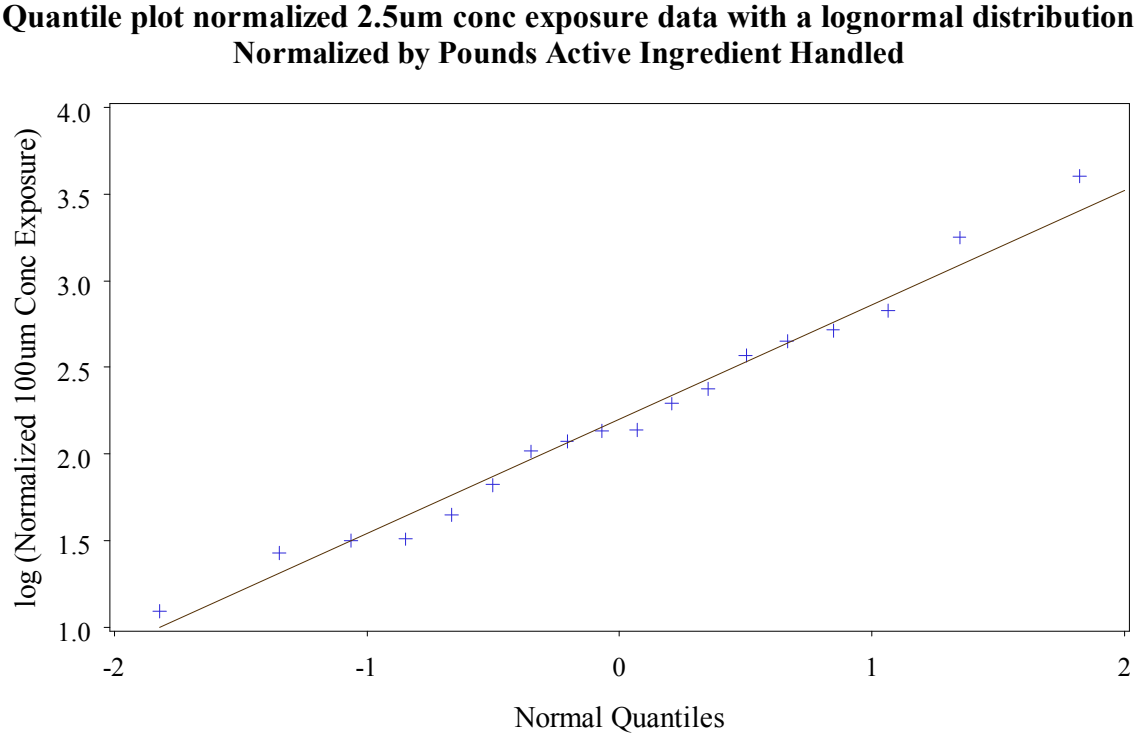
Quantile plot normalized 2.5um conc exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 100um Conc Exposure)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
-2
-1
0
1
2
Normal Quantiles

Figure 16

These statistical models for the normalized exposure assume that the exposure is proportional to the normalizing variable pounds of active ingredient handled. More precisely, the assumed statistical models are of the form

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error Terms

where Slope = 1. Possible alternative models include the same formulation with a Slope of zero, implying that the exposure does not depend upon the amount of active ingredient handled, even though the amount of active ingredient handled varied between the subjects as part of the study design. Other possible models include the same model with a slope not equal to zero or one, the quadratic models discussed below, or models with more complicated relationships between the exposure and the experimental conditions. To evaluate whether the slope is zero, one, or other possible values, we fitted the above statistical model and computed confidence intervals for the slope. In the appendix we investigate normalizing by the spraying duration.

To analyze the proportionality, we also considered an additional hypothetical clothing scenario with no clothing at all. The dermal exposure for the No clothing scenario was calculated by summing all the inner and outer dermal exposure measurements:

All Dermal. This case represents the dermal exposure for a subject wearing no clothes. The exposure is the sum of the mass from hand wash, face and neck, and the six inner and six outer dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

We can use these statistical models to calculate confidence intervals for the slope. The calculation of the confidence intervals depends upon the value of the denominator degrees of freedom for the mixed models used. A review of the alternative methods for calculating the denominator degrees of freedom for fixed effects in a mixed model using the SAS MIXED procedure is given in an article by Schaalje et al[1]. Based on that article, the following Table 12 summarizes the five available methods:

Table 12. SAS Methods for Computing the Fixed Effects Denominator Degrees of Freedom in PROC MIXED.

DDF Method	**SAS Abbreviation**	**Comments**
Residual	residual	Uses residual degrees of freedom. Ignores covariance structure as defined by the RANDOM and REPEATED statements. This method is not recommended.
Containment	contain	Default method when RANDOM statements are present. Accounts for the minimum contribution of the random effects that syntactically

[1] Schaalje, G. B., J. B. McBride, G. W. Fellingham. "Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED" *Proceedings of the Twenty Sixth Annual SAS Users Group International Conference*. April 2001. Long Beach, CA. ISBN 1-58025-864-6. SAS Institute, Cary, NC 27513.

DDF Method	SAS Abbreviation	Comments
		contain the fixed effects of interest.
Between-Within	bw	Default method when REPEATED statements are present and RANDOM statements are not present. Only exact when the data are balanced and the design is a repeated measures design with compound symmetry, and where the levels of the within-subjects effects are not replicated within any of the subjects. Otherwise the method is at best approximate and can be unpredictable.
Satterthwaite / Fai-Cornelius	satterth	Designed to approximate the denominator degrees of freedom for split-plot designs with complicated covariance structures and/or unbalanced data sets.
Kenwood-Rogers	kr	Designed to approximate the denominator degrees of freedom for designs with complicated covariance structures and/or unbalanced data sets. Results from simulations suggest better performance than the Satterthwaite method. If a covariance parameter has zero variance then this method ignores that covariance.

To interpret this table for this study, note that the RANDOM statement was used to define the cluster effect. If the ICC equals zero, then there is no clustering and the cluster variance equals zero. The REPEATED statement was used to define the repeated measures model. A balanced data set is one where each treatment combination is applied to the same number of subjects. For this study, this implies that there are the same number of workers in every cluster, and each worker has the same number of measured exposure values.

The study data were balanced since there were 6 workers in each cluster, each with the same number of exposure measurements. Based on this summary, the recommended methods are the containment method for the mixed models when the ICC parameter is zero, and the Kenwood-Rogers method for the mixed models where the ICC parameter is non-zero or for the repeated measures model (detailed below). (For other applications, the Kenwood-Rogers method would be preferred in general if the data are sufficiently unbalanced, but it is not easy to provide rules as to how this should be defined.) The confidence intervals for the regression coefficients presented in this memorandum follow these recommendations. In particular, since the ICC parameters in the mixed regression models for the logarithm of the long

dermal, short dermal, long short dermal, all hands, and inhalation exposure against the logarithm of the pounds of active ingredient handled were all zero, the containment method was used in those cases. However, since the ICC parameter in the mixed regression models for the logarithm of the all dermal exposure against the logarithm of the pounds of active ingredient handled was non-zero, although the value was only 0.002, the Kenwood-Rogers method was used for that mixed model. Note that this issue does not impact the calculated confidence intervals for the summary statistics in Tables 4 to 11, since they were based on a bootstrap method.

Table 13 shows the 95% confidence intervals for the slope calculated from the above model, either assuming the lognormal simple random sampling model for the errors or the lognormal mixed model for the errors. Also shown is the width of the confidence interval for the slope. A confidence interval that includes one but not zero supports the assumptions of the normalized exposure models. A confidence interval that includes zero but not one suggests that the exposure does not depend on the amount of active ingredient handled. A confidence interval that includes both zero and one suggests that either the basic statistical model is incorrect or there are not enough data to statistically infer whether the slope is zero or one. The Repeated Measures statistical model (bottom row) is described and discussed below. Regression models for the filter measurements by size fraction are not presented in this memorandum.

Table 13. 95 percent confidence intervals for the slope of log exposure versus log pounds active ingredient handled.

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	Mixed	0.81	0.08	1.54	1.47
		Simple Linear	0.81	0.08	1.53	1.45
	Short pants and short sleeves	Mixed	1.01	0.47	1.55	1.07
		Simple Linear	1.01	0.48	1.54	1.06
	Long pants and short sleeves	Mixed	0.87	0.25	1.48	1.24
		Simple Linear	0.87	0.26	1.48	1.22
	Hands Only	Mixed	0.70	-0.01	1.40	1.40
		Simple Linear	0.70	0.00	1.39	1.39
	None	Mixed	1.02	0.55	1.49	0.94
		Simple Linear	1.02	0.56	1.48	0.92
Inhalation (mg/m^3)		Mixed	0.43	-0.11	0.97	1.08
		Simple Linear	0.43	-0.11	0.96	1.07

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Any	Repeated Measures	1.28	0.78	1.77	0.99

For all of the dermal exposure cases except for the mixed model for hands only, the confidence interval for the slope includes 1 but not 0. Thus, for these cases, the assumption of proportionality was not rejected and the assumption of independence was rejected. For the mixed model for hands only, the confidence interval for the slope includes both 1 and 0 (although the lower bound is nearly zero, so that the assumptions of proportionality and independence were both not rejected. For the inhalation exposure, there is sufficient evidence to reject the hypothesis of a slope of 1 at the 5% significance level.

A few of the slope values in Table 13 are slightly above 1. Since the confidence intervals include 1, these cases provide good support for the proportionality assumption. As discussed below, when the slope is greater than one, the predicted means from the normalized exposure model will underestimate the predicted means from the mixed model with an estimated slope (of the log exposure against the log amount of active ingredient) when the amount of active ingredient is high. However, this underestimation will be negligible when the slope is only slightly above 1, except if the amount of active ingredient handled is extremely high.

Based on the available CMA data, the experiment was designed to be able to detect whether the slope was 0 or 1 using a test at the 5% significance level with a power of 80%. On that basis, the experiment was designed to make the expected confidence interval width equal to 1.4:

Given:

Power = 1 – P(type II error) = $1-\beta = 0.80$;

Significance level = P(type I error) = $\alpha = 0.05$;

(Eq. 1) Predicted 95% Confidence Interval (two sided) for the regression slope = Sample estimate of slope ± 1.96× Standard Error

Effect Size = $(Z_{1-\alpha/2} + Z_{1-\beta}) \times$ Standard Error

Here, Z_P is the p^{th} percentile of a standard normal distribution:

$Z_{1-\alpha/2} = Z_{0.975} = 1.96$;

$Z_{1-\beta} = Z_{0.80} = 0.84$

$Z_{1-\alpha/2} + Z_{1-\beta} = 2.8$

(Eq. 2) Standard Error = Effect Size ÷ 2.8

Substituting Standard Error into (Eq. 1):

Predicted 95% Confidence Interval (two sided) for the regression slope = Sample estimate ± 1.96× (Effect Size ÷ 2.8) = Sample estimate ± 0.7×Effect Size

Here, Effect Size = 1 – 0 = 1 (i.e., slope = 1 under H_1 vs. slope = 0 under H_0)

So, expected width of confidence interval for slope parameter = 2×0.7 = 1.4

The results in Table 13 show that the actual confidence interval widths were less than 1.4 for all the exposure cases except for the long pants and long sleeves scenario where the width was slightly higher, 1.5.

For the simple linear regression analyses based on the simple random sampling model, the relationship between the exposure and the amount of active ingredient is displayed in the following regression plots in Figures 17 to 22.

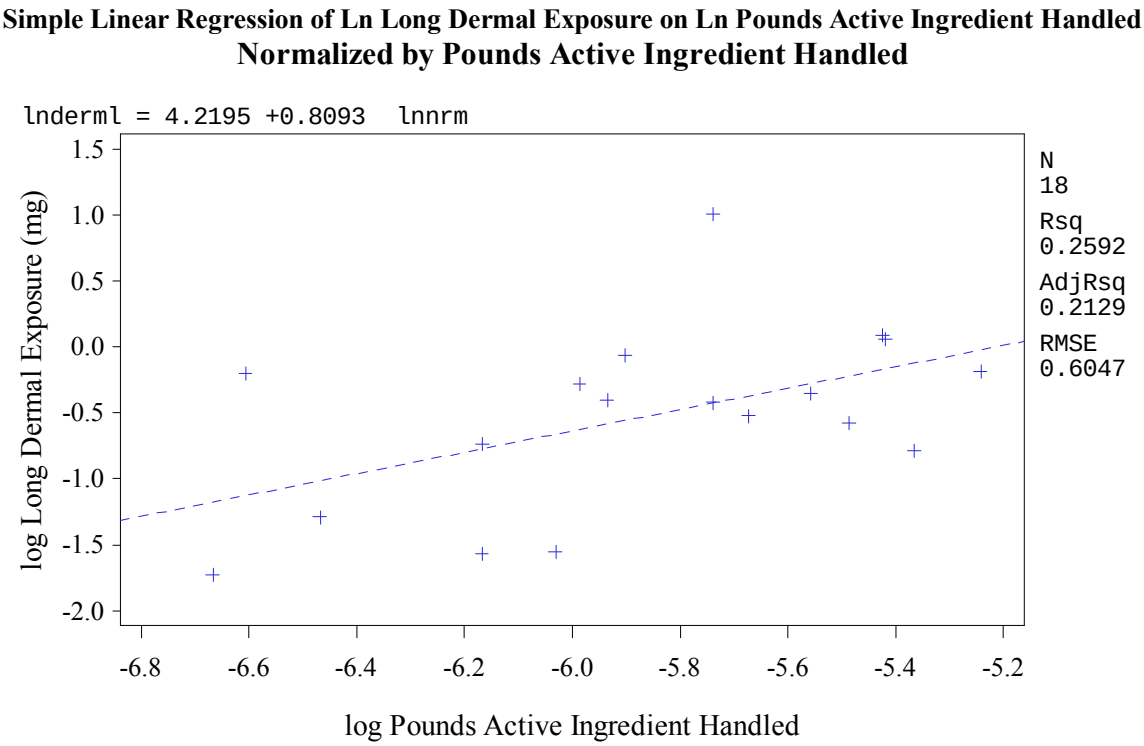

Figure 17

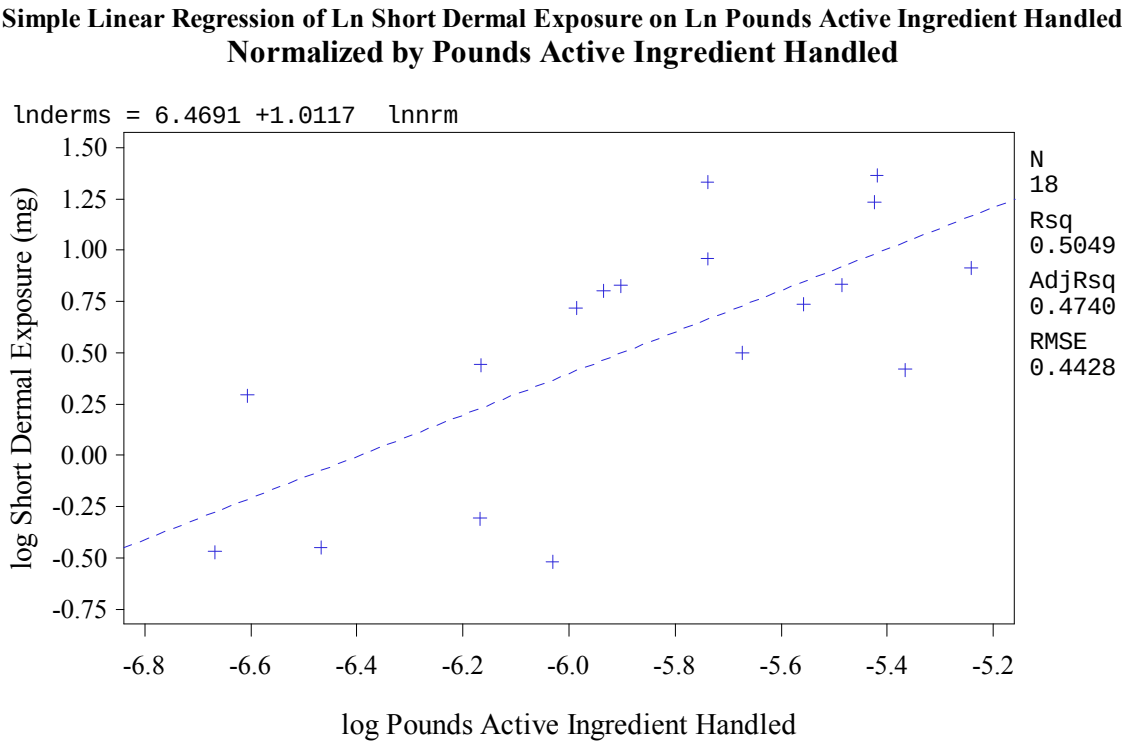
Simple Linear Regression of Ln Short Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lnderms = 6.4691 +1.0117 lnnrm
N
18
Rsq
0.5049
AdjRsq
0.4740
RMSE
0.4428
log Short Dermal Exposure (mg)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-6.8
-6.6
-6.4
-6.2
-6.0
-5.8
-5.6
-5.4
-5.2
log Pounds Active Ingredient Handled

Figure 18

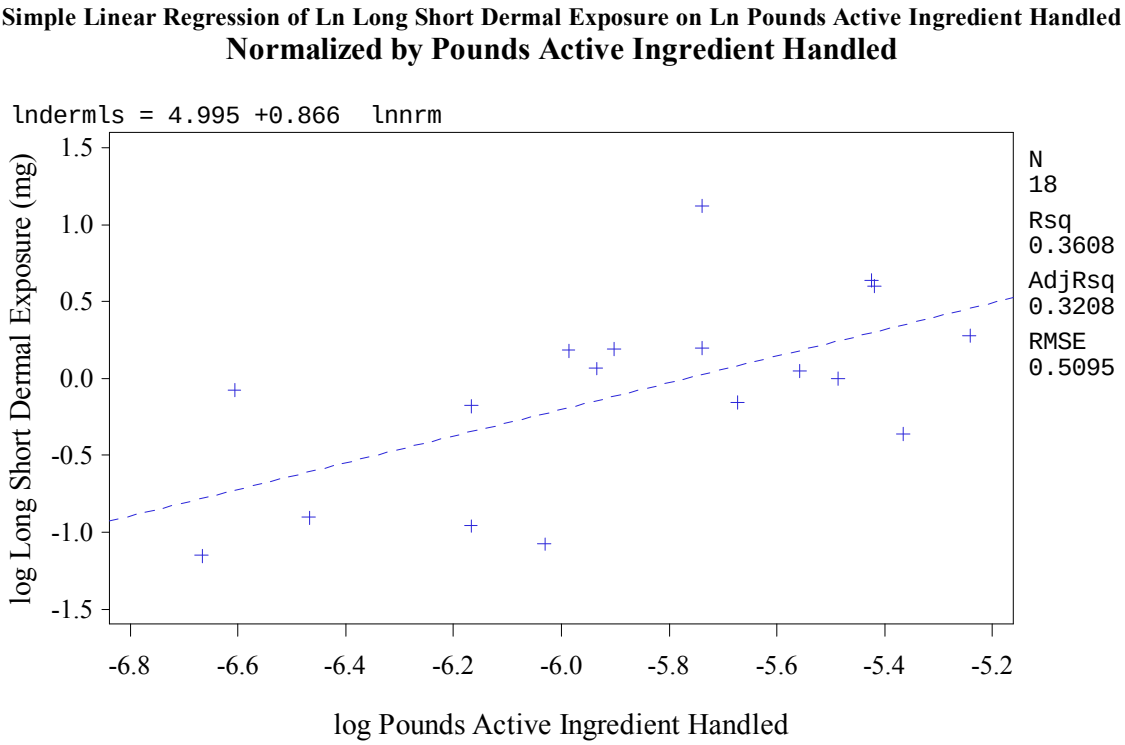
Simple Linear Regression of Ln Long Short Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lndermls = 4.995 +0.866 lnnrm
log Long Short Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-6.8
-6.6
-6.4
-6.2
-6.0
-5.8
-5.6
-5.4
-5.2
log Pounds Active Ingredient Handled
N
18
Rsq
0.3608
AdjRsq
0.3208
RMSE
0.5095

Figure 19

Simple Linear Regression of Ln All Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled

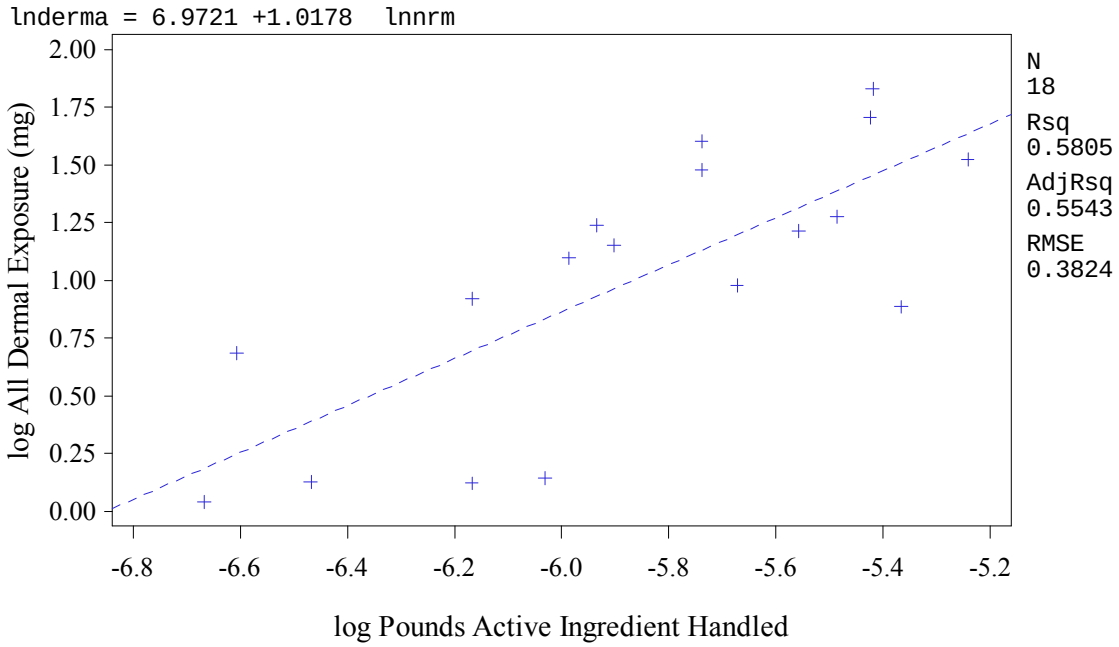

Figure 20

Simple Linear Regression of Ln Hands Only Exposure on Ln Pounds Active Ingredient Handled Normalized by Pounds Active Ingredient Handled

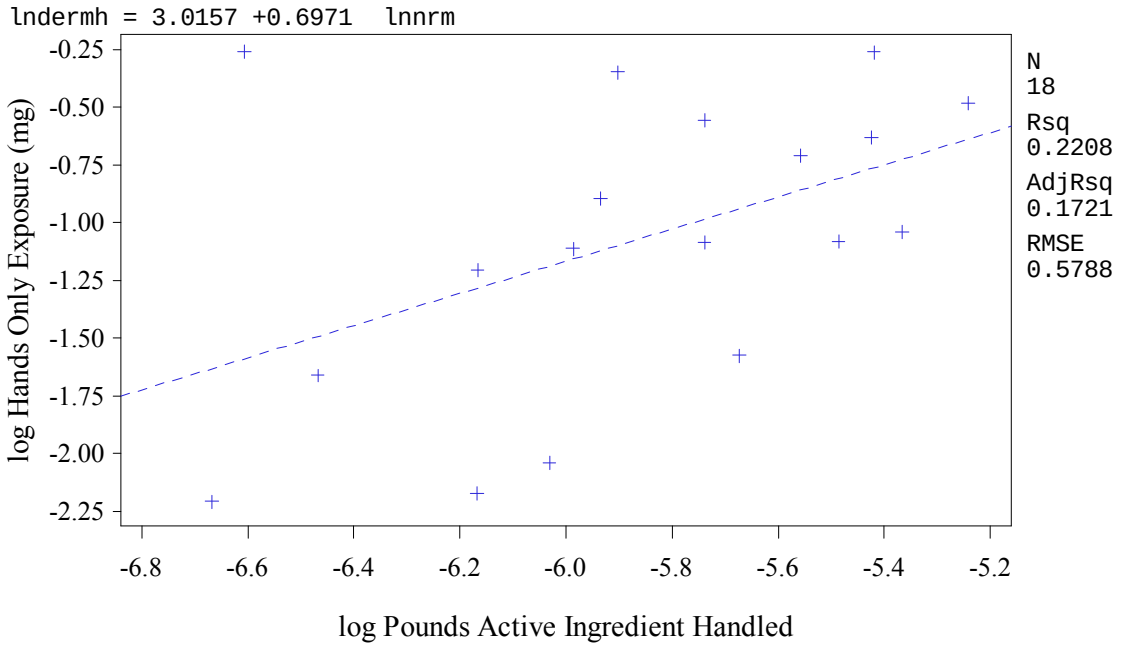

Figure 21

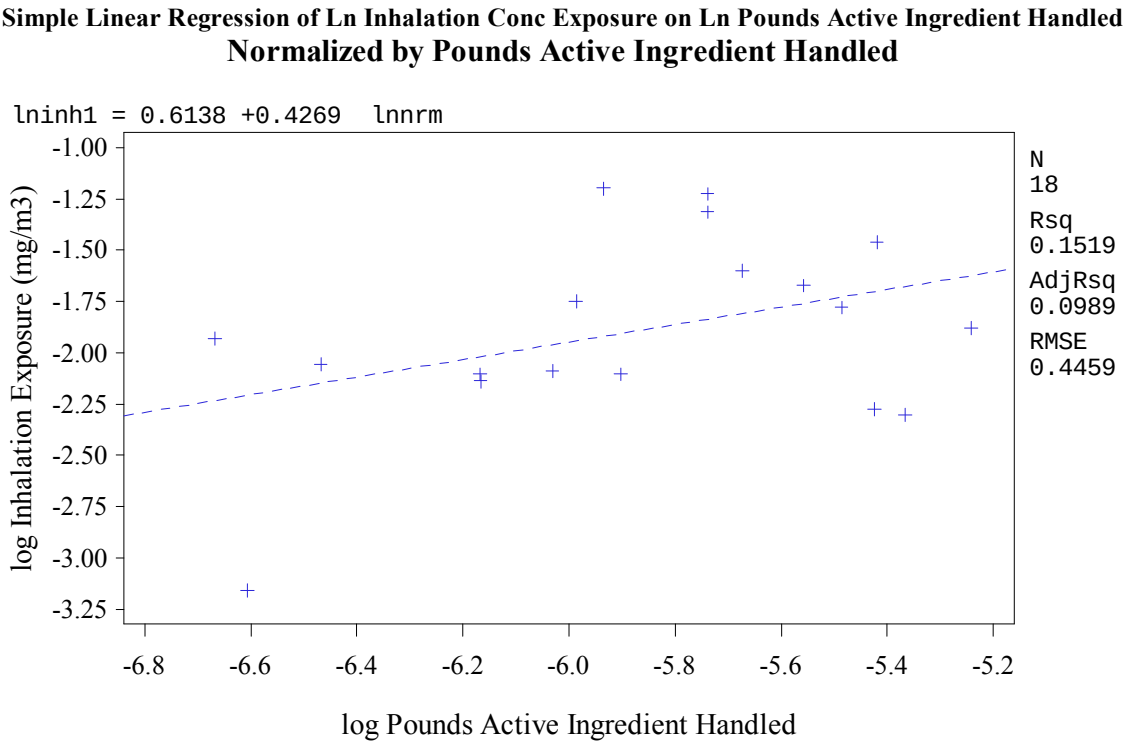
Simple Linear Regression of Ln Inhalation Conc Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lninh1 = 0.6138 +0.4269 lnnrm
N
18
Rsq
0.1519
AdjRsq
0.0989
RMSE
0.4459
log Inhalation Exposure (mg/m3)
-1.00
-1.25
-1.50
-1.75
-2.00
-2.25
-2.50
-2.75
-3.00
-3.25
-6.8
-6.6
-6.4
-6.2
-6.0
-5.8
-5.6
-5.4
-5.2
log Pounds Active Ingredient Handled

Figure 22

These simple linear regression results are compared with the results for the lognormal mixed models in Figures 23 to 28. In all these cases, the regression lines are the same for the mixed and simple linear regression models because the estimated ICC parameter was zero. Although these regression lines in these figures and the same as in Figures 17 to 22, they are included for consistency with the previous reviews.

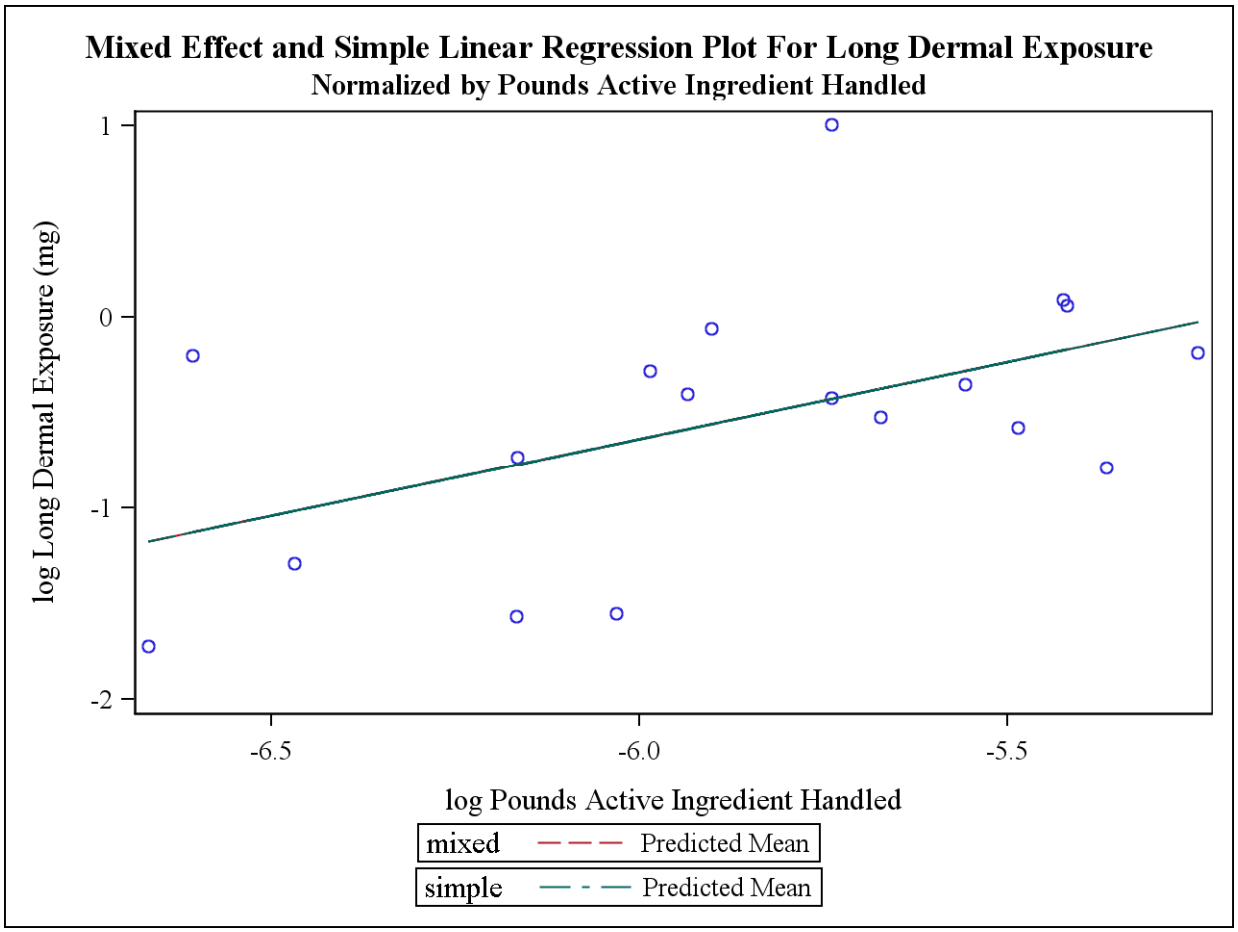

Figure 23

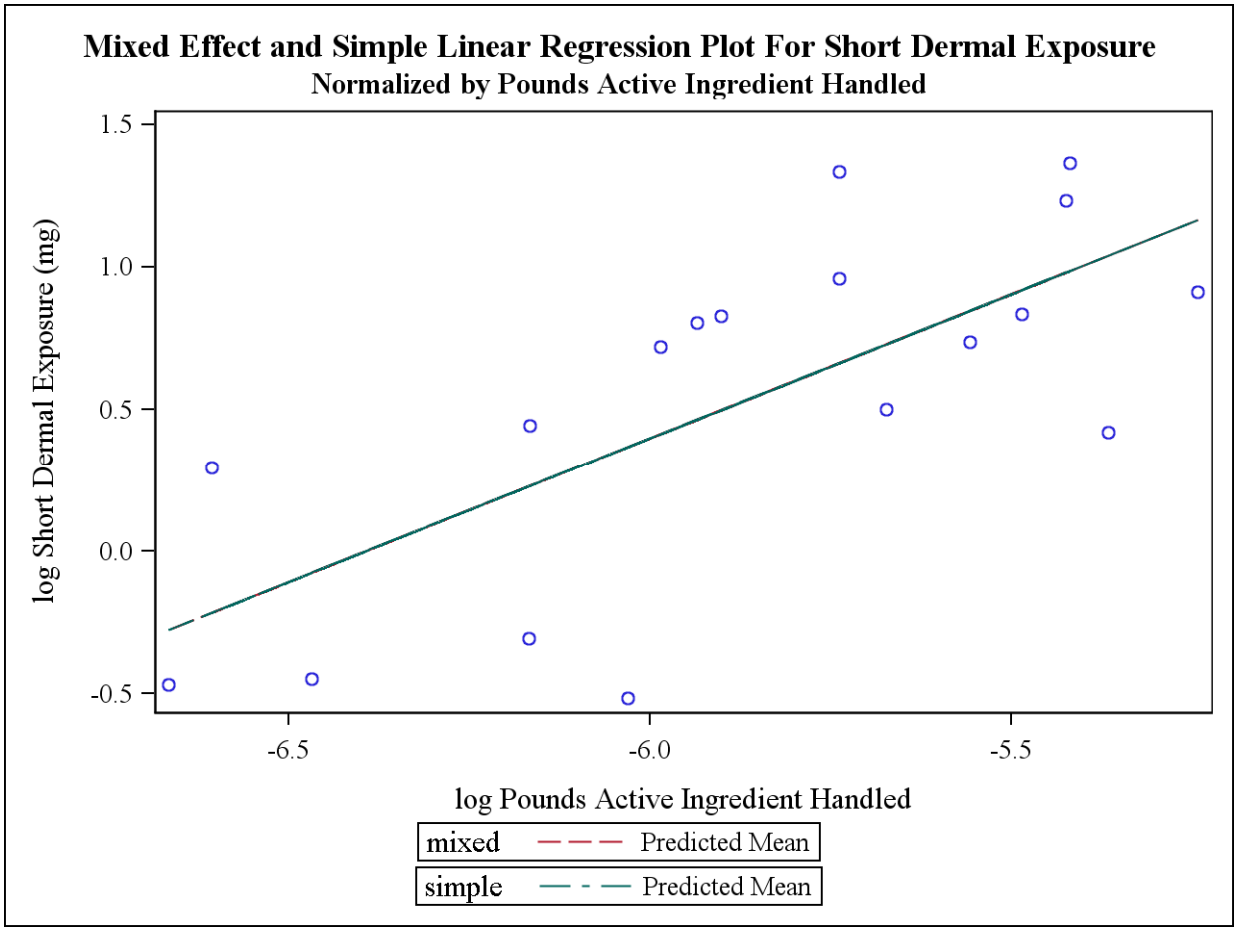
Mixed Effect and Simple Linear Regression Plot For Short Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log Short Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed
Predicted Mean
simple
Predicted Mean

Figure 24

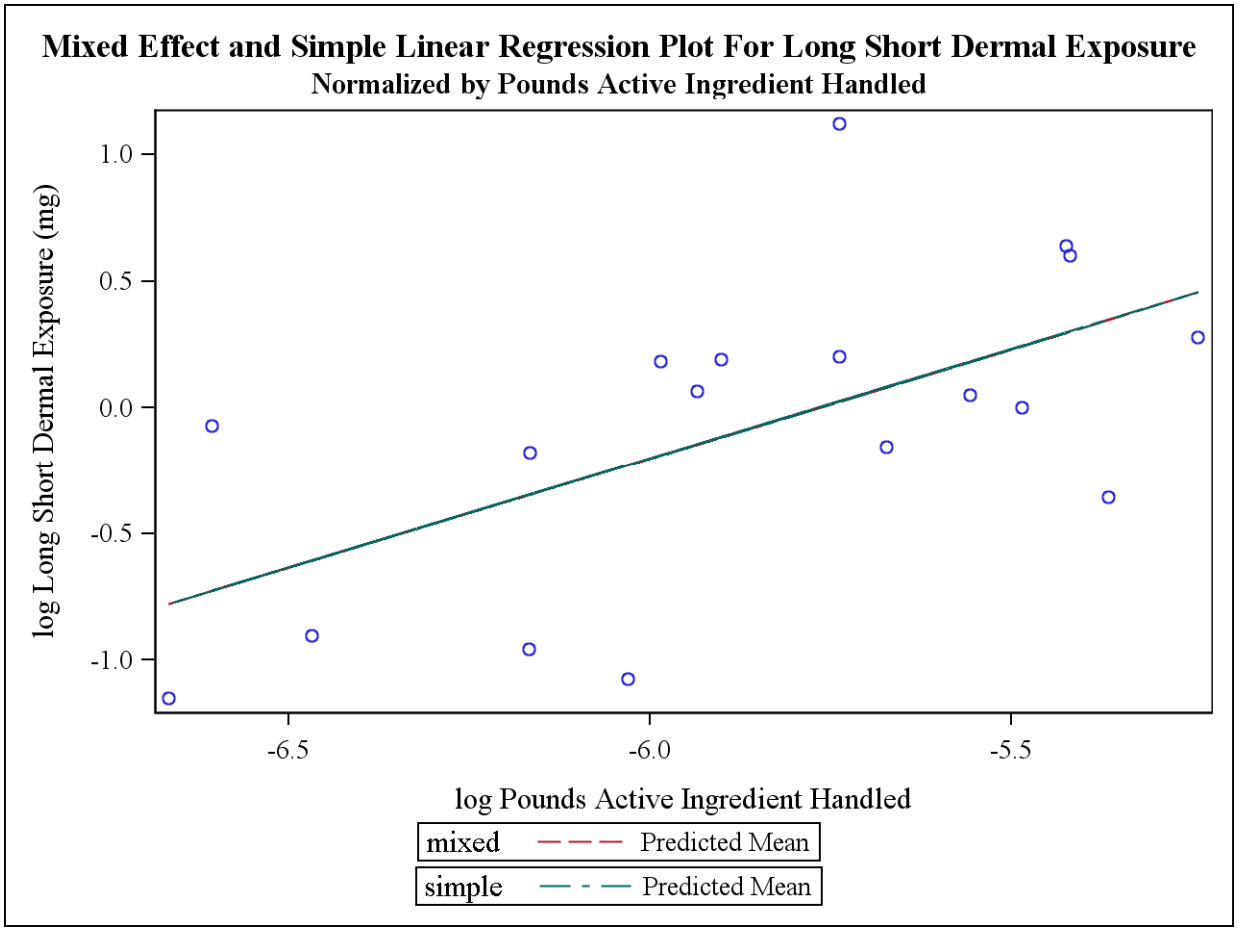
Mixed Effect and Simple Linear Regression Plot For Long Short Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log Long Short Dermal Exposure (mg)
1.0
0.5
0.0
-0.5
-1.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 25

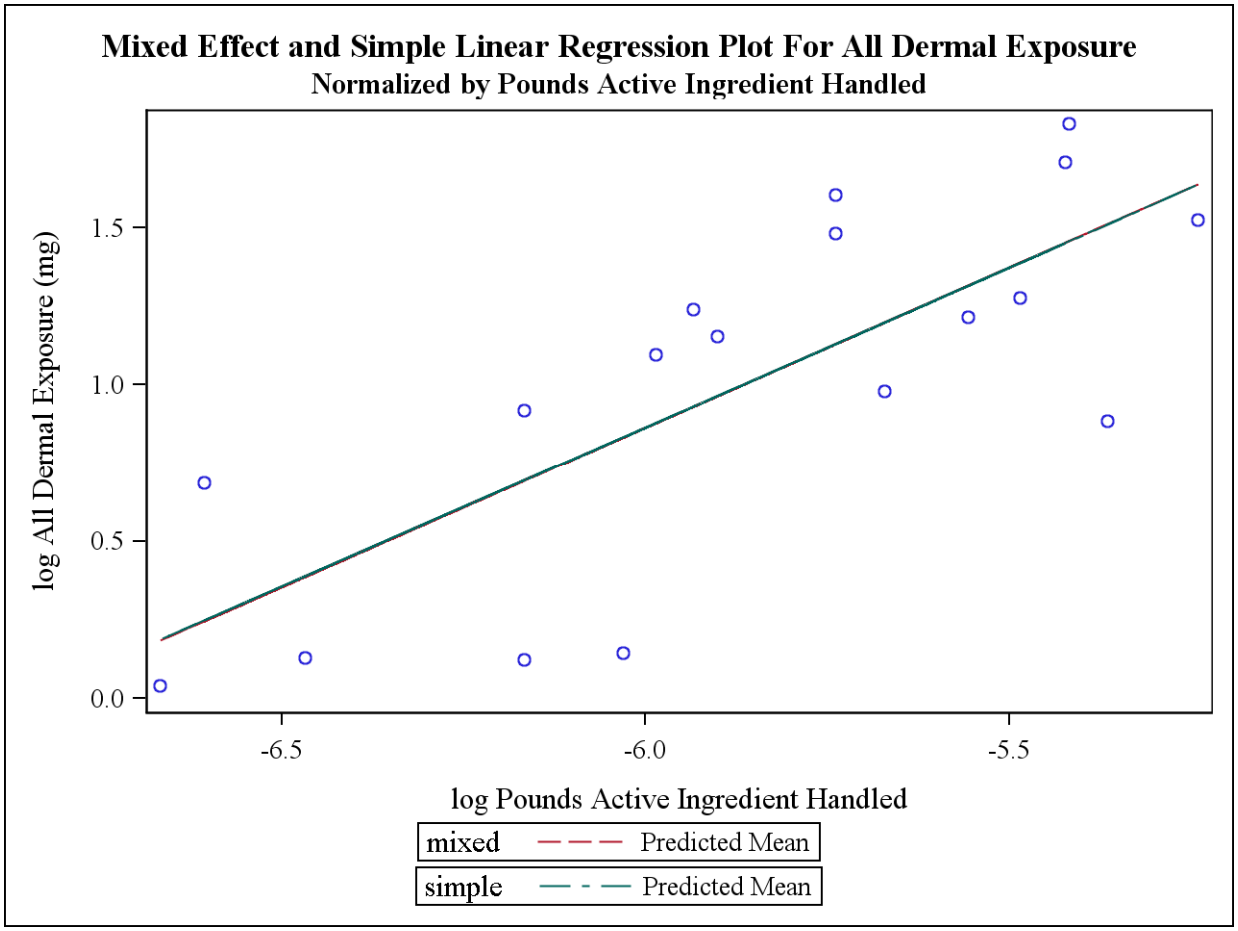
Mixed Effect and Simple Linear Regression Plot For All Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log All Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 26

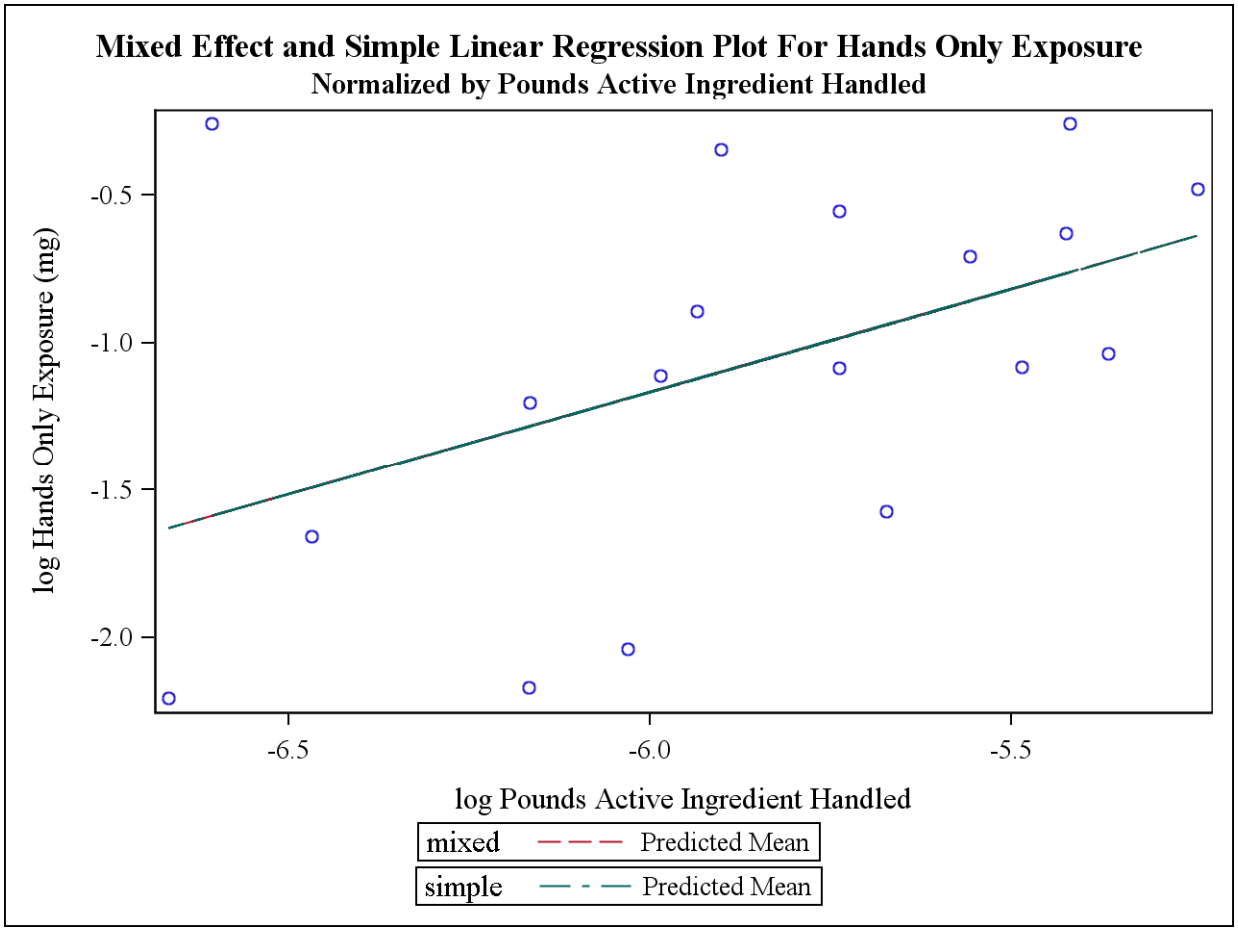
Mixed Effect and Simple Linear Regression Plot For Hands Only Exposure
Normalized by Pounds Active Ingredient Handled
log Hands Only Exposure (mg)
-0.5
-1.0
-1.5
-2.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 27

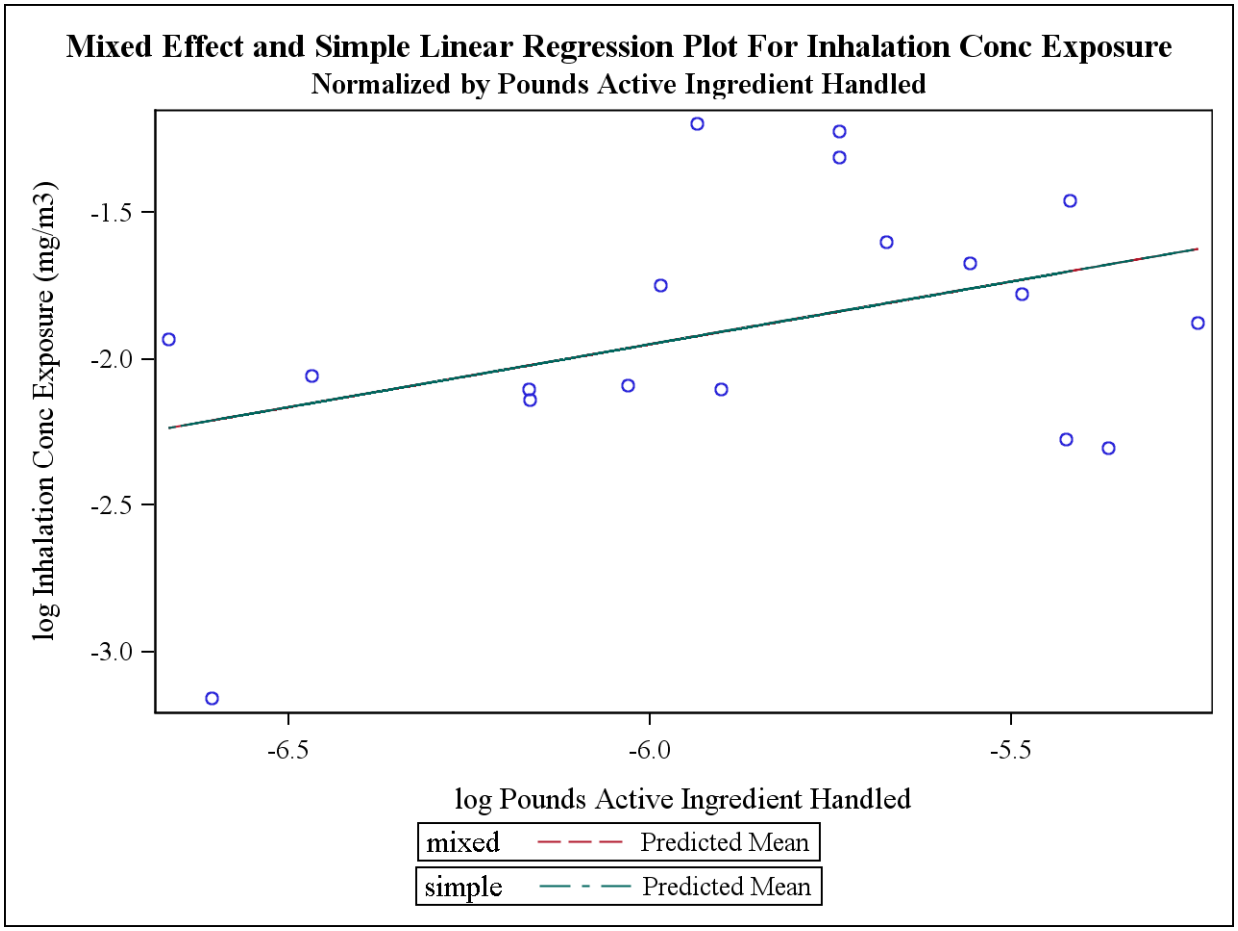
Mixed Effect and Simple Linear Regression Plot For Inhalation Conc Exposure
Normalized by Pounds Active Ingredient Handled
log Inhalation Conc Exposure (mg/m3)
-1.5
-2.0
-2.5
-3.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed
Predicted Mean
simple
Predicted Mean

Figure 28

Finally, in Figure 29 we present a regression plot showing the slightly different regression lines for the three clusters based on the mixed model for all dermal exposure. For the other dermal clothing configurations and the inhalation exposure, the mixed models predict the same values for all three clusters.

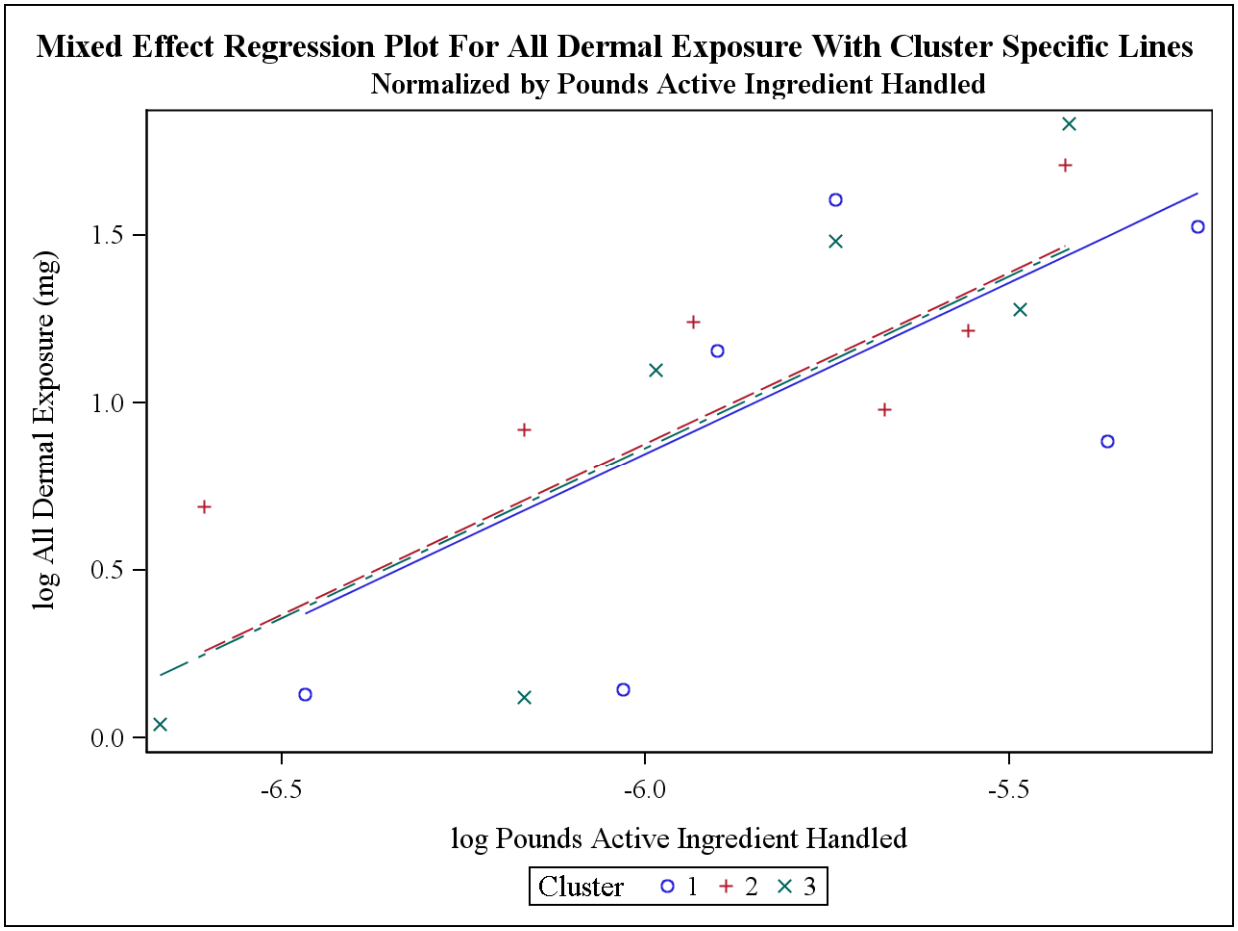

Figure 29

The above analyses of the proportionality for dermal exposure consistently show similar positive slopes, as one might expect on physical grounds. All of the estimated slopes for dermal exposure are positive and approximately 0.8, and all the confidence intervals contained 1. To investigate this issue further, the following more complicated statistical model was fitted to the data of all three dermal exposures (excluding the unrealistic hands only and no clothing case) for all 18 subjects. The model was of the form:

Log (dermal exposure) = LnGM (clothing type) + Slope × Log (Pounds of Active Ingredient) + Cluster + Error

In this model, the intercept depends upon the clothing type, so there are three intercepts. The slope is the same for all three clothing types, The Cluster term accounts for possible clustering effects due to the location. Finally, to account for the expected correlations between different dermal exposure measurements on the same worker, the three error terms (one per clothing type) for each worker are assumed to be correlated (with an unspecified covariance matrix), but errors for different workers are assumed to be independent. Thus in SAS terminology, the Cluster effect is a RANDOM

effect and the Error is a REPEATED effect where the subject is the worker. We will call this model the "Repeated Measures" model. The confidence interval for the slope using this statistical model is shown in the bottom row of Table 13. Since the confidence interval includes one and does not include zero, the proportionality for dermal exposure has been shown using this statistical model.

Quadratic models

The proportionality test was based on a linear model for log exposure versus log pounds active ingredient handled. The HSRB suggested that a quadratic model should also be considered.

There are two quadratic models that could be considered. Since the original linear model is of the form

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error Terms,

the main quadratic model is of the form

Log (Exposure) =

Intercept + Slope × Log (Pounds of Active Ingredient) +
Quad × {Log (Pounds of Active Ingredient)}^{2} + Error Terms.

Note that the quadratic term is the square of the logarithm of the pounds of active ingredient rather than the logarithm of the square; the latter approach produces an ill-defined model with two multiples of the logarithm of the pounds of active ingredient.

Another approach might be to consider a quadratic model for exposure:

Exposure =

Intercept + Slope × (Pounds of Active Ingredient) +
Quad × (Pounds of Active Ingredient)^2 + Error Terms.

We do not recommend this second approach for these data since the exposures are known to be non-negative and the quantile plots indicate that the exposure data are better modeled using a log-normal distribution than using a normal distribution. Furthermore, unless the intercept is zero, this model predicts a nonzero exposure when the pounds of active ingredient is zero, and so a more realistic (though possibly poorer-fitting) model of this form would have a zero intercept. For other exposure data a proportionality test could be carried out by fitting the zero intercept model

Exposure = Slope × (Pounds of Active Ingredient) + Quad × (Pounds of Active Ingredient)^2 + Error Terms

and testing if Quad equals zero.

The parsimony principle suggests that the appropriate statistical procedure for this study is to first fit the quadratic regression model for the logarithm of the exposure

Log (Exposure) =

Intercept + Slope × Log (Pounds of Active Ingredient) +
Quad × {Log (Pounds of Active Ingredient)}^{2} + Error Terms.

If the coefficient Quad is statistically significant at the 5% level, which is equivalent to requiring that the 95% confidence interval does not include zero, than the quadratic model is supported. Otherwise the linear model should be used.

Table 14 presents the fitted quadratic models from the study for the mixed models of five exposure measurements (Long Dermal, Short Dermal, Long Short Dermal, Hands Only, Inhalation) and for the Repeated Measures model for Dermal exposures. For the Repeated Measures model, the model has different intercepts (but the same Slope and Quad coefficients) for the three different dermal exposures. In view of the earlier discussion about denominator degrees of freedom, the confidence intervals for cases where the ICC parameter is non-zero and for the Repeated Measures model are calculated using the Kenwood-Rogers method. The confidence intervals for other cases where the ICC parameter is zero are calculated using the containment method.

Table 14. Quadratic mixed models with 95% confidence intervals for the log exposure versus log pounds active ingredient handled.

Exposure	**Parameter**	**Estimate**	**Degrees of Freedom**	**Lower Bound**	**Upper Bound**	**GSD**	**ICC**	**Width of Confidence Interval**
Long Dermal	Intercept	-9.04	2.00	-137.34	119.27	1.86	0.00	256.61
Long Dermal	Slope	-3.67	13.00	-25.37	18.04	1.86	0.00	43.41
Long Dermal	Quad	-0.38	13.00	-2.20	1.45	1.86	0.00	3.64
Short Dermal	Intercept	-4.86	2.00	-98.59	88.86	1.57	0.00	187.45
Short Dermal	Slope	-2.81	13.00	-18.67	13.04	1.57	0.00	31.71
Short Dermal	Quad	-0.32	13.00	-1.65	1.01	1.57	0.00	2.66
Long Short Dermal	Intercept	-7.96	2.00	-115.82	99.90	1.68	0.00	215.72
Long Short Dermal	Slope	-3.51	13.00	-21.75	14.74	1.68	0.00	36.49

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Long Short Dermal	Quad	-0.37	13.00	-1.90	1.16	1.68	0.00	3.06
Hands Only	Intercept	20.71	2.00	-101.33	142.75	1.80	0.00	244.08
Hands Only	Slope	6.67	13.00	-13.98	27.31	1.80	0.00	41.29
Hands Only	Quad	0.50	13.00	-1.23	2.23	1.80	0.00	3.46
Inhalation	Intercept	-38.66	13.19	-81.35	4.03	1.51	0.00	85.39
Inhalation	Slope	-12.83	13.18	-27.21	1.55	1.51	0.00	28.76
Inhalation	Quad	-1.11	13.17	-2.32	0.09	1.51	0.00	2.41
Dermal Repeated Measures	Slope	-1.29	12.63	-15.98	13.41	NA	NA	29.39
Dermal Repeated Measures	Quad	-0.21	12.62	-1.45	1.02	NA	NA	2.46

Since the 95% confidence intervals for Quad include zero in every case, the quadratic coefficient is not statistically significant and the quadratic models are not supported.

Threshold Analyses

As described above, the following two mixed models were fitted to the dermal and inhalation exposure data.

Linear mixed model:

Log (Exposure) = Intercept1 + Slope × Log (Pounds of Active Ingredient) + Cluster + Error

Normalized exposure mixed model:

Log (Exposure) = Intercept2 + Log (Pounds of Active Ingredient) + Cluster + Error,

which is mathematically the same as

Log (Exposure/Pounds of Active Ingredient) = Intercept2 + Cluster + Error

The intercepts for these two models are denoted as Intercept1 and Intercept2 since their estimated values will in general be different.

Cluster is a normally distributed random effect variable with independent, identically distributed values for each cluster, and Error is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. If the linear mixed model has a slope of 1, then the model is mathematically the same as the normalized exposure mixed model.

These two statistical models can be compared by calculating the threshold value of the pounds of active ingredient at which both models predict the same mean exposure. The threshold values are computed as follows.

Suppose first that the linear mixed model for log Exposure is correct. Then the predicted mean exposure for a given amount of active ingredient is given by the equation

Predicted mean exposure from linear mixed model =

$$\exp(\text{Intercept1}) \times (\text{Pounds of Active Ingredient})^{\text{Slope}} \times \exp(\tfrac{1}{2}\, V1) \qquad (1)$$

where V1 is the total variance for the linear mixed model, calculated as the sum of the cluster variance and the error variance. The predicted mean exposure is the expected value of the exposure for a given amount of active ingredient and thus estimates the average (arithmetic mean) exposure for a large number of scenarios that are all using the same amount of active ingredient.

Suppose instead that the normalized exposure mixed model for log Exposure is correct. Then the predicted mean exposure is given by the equation

Predicted mean exposure from normalized exposure mixed model =

$$\exp(\text{Intercept2}) \times (\text{Pounds of Active Ingredient}) \times \exp(\tfrac{1}{2}\, V2) = AMm \times \text{Pounds of Active Ingredient} \qquad (2)$$

where V2 is the total variance for the normalized exposure mixed model, calculated as the sum of the cluster variance and the error variance. AMm is the estimated average normalized exposure,

$$AMm = \exp(\text{Intercept2} + \tfrac{1}{2}\, V2)$$

We now have two estimates of the predicted mean exposure for a given amount of active ingredient, equations (1) and (2). The graphs in Figures 30 to 34 below compare the predicted means for each clothing configuration (Long Dermal, Short Dermal, Long Short Dermal, Hands Only) and for total inhalation exposure. The two estimates (1) and (2) are equal if the pounds of active ingredient equals the Threshold value:

$$\text{Threshold} = \{AMm / \exp(\text{Intercept1} + \tfrac{1}{2}\, V1)\}^{1/(\text{Slope} - 1)}$$

The Threshold values are tabulated in Table 15 below.

Suppose that the estimated slope is less than 1 (which is true for all the cases studied here except for the Short Dermal exposure which had an estimated slope slightly greater than 1). The predicted mean exposure from the normalized exposure mixed model will be greater than the predicted mean exposure from the linear mixed model for amounts of active ingredient above the threshold (right hand side of the graph). The predicted mean exposure from the normalized exposure mixed model will be less than the predicted mean exposure from the linear mixed model for amounts of active ingredient below the threshold (left hand side of the graph). What this means is that if we assume proportionality and use the normalized exposure mixed model, then we will tend to over-predict the exposure unless the amount of active ingredient is below the threshold. (If the amount of active ingredient is below the threshold, then it will be low enough that the exposure will not usually be of concern).

For the Short Dermal exposure, the estimated slope was greater than one. In this exceptional case the inequalities are reversed: The predicted mean exposure from the normalized exposure mixed model will be greater than the predicted mean exposure from the linear mixed model for amounts of active ingredient below the threshold (left hand side of the graph). The predicted mean exposure from the normalized exposure mixed model will be less than the predicted mean exposure from the linear mixed model for amounts of active ingredient above the threshold (right hand side of the graph). Although this case shows a tendency for exposure estimates from the normalized exposure mixed model to under-predict exposure, it is clearly seen from the graph that the two curves are numerically extremely close so that the under-prediction is very small.

Table 15. Threshold values for the amount of active ingredient.

Exposure Route	**Clothing**	**Model**	**Slope**	**Threshold Level (lb active ingredient)**
Dermal (mg)	Long pants and long sleeves	Mixed	0.81	0.00295
	Short pants and short sleeves	Mixed	1.01	0.00174*
	Long pants and short sleeves	Mixed	0.87	0.00297
	Hands only	Mixed	0.70	0.00285
Inhalation (mg/m3)		Mixed	0.43	0.00272

*For this case, slope > 1 and so the normalized exposure mixed model under-predicts exposure for pounds of active ingredient above the threshold.

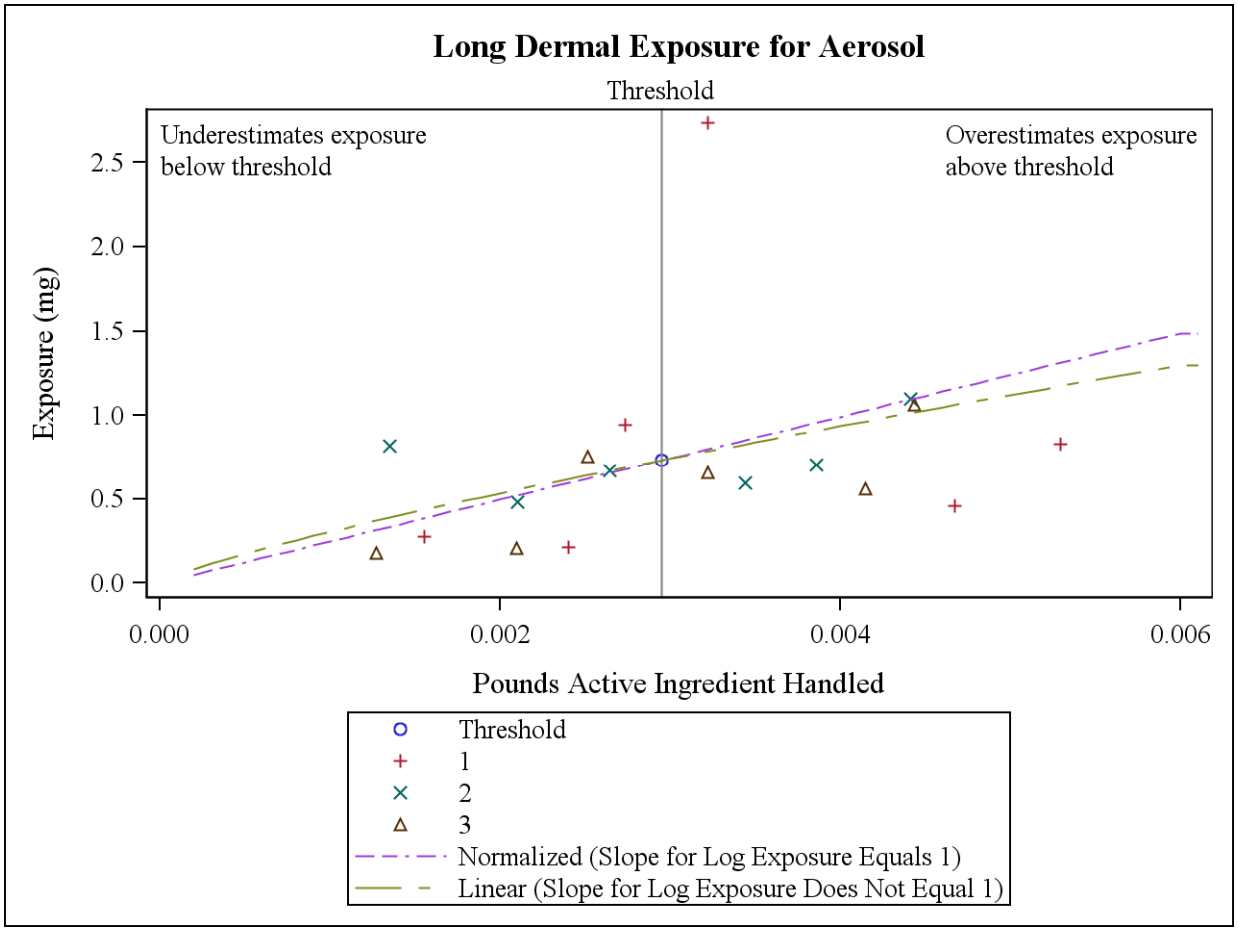
Long Dermal Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
2.5
2.0
1.5
1.0
0.5
0.0
0.000
0.002
0.004
0.006
Pounds Active Ingredient Handled
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 30

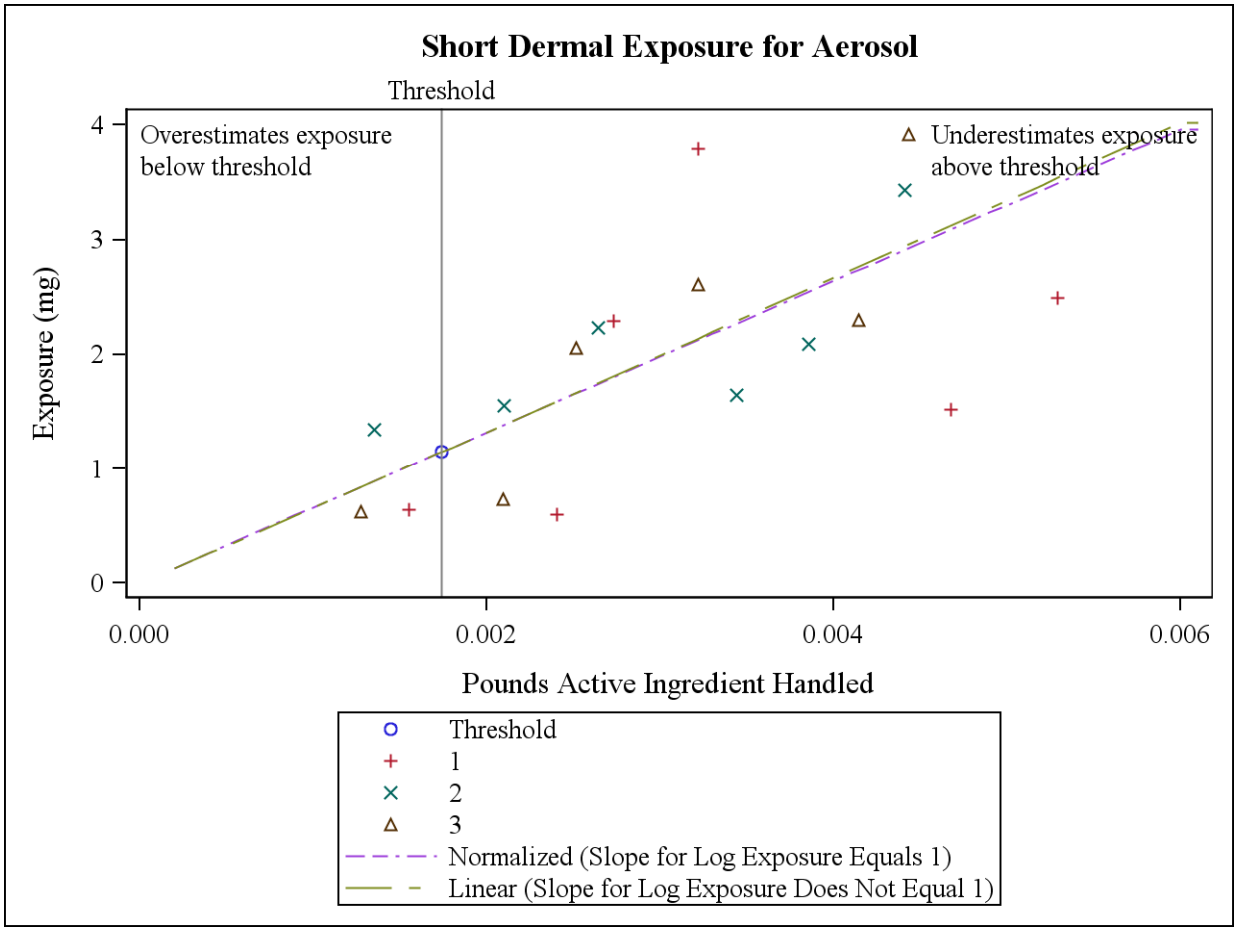
Short Dermal Exposure for Aerosol
Threshold
Overestimates exposure below threshold
Underestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.000
0.002
0.004
0.006
Pounds Active Ingredient Handled
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 31

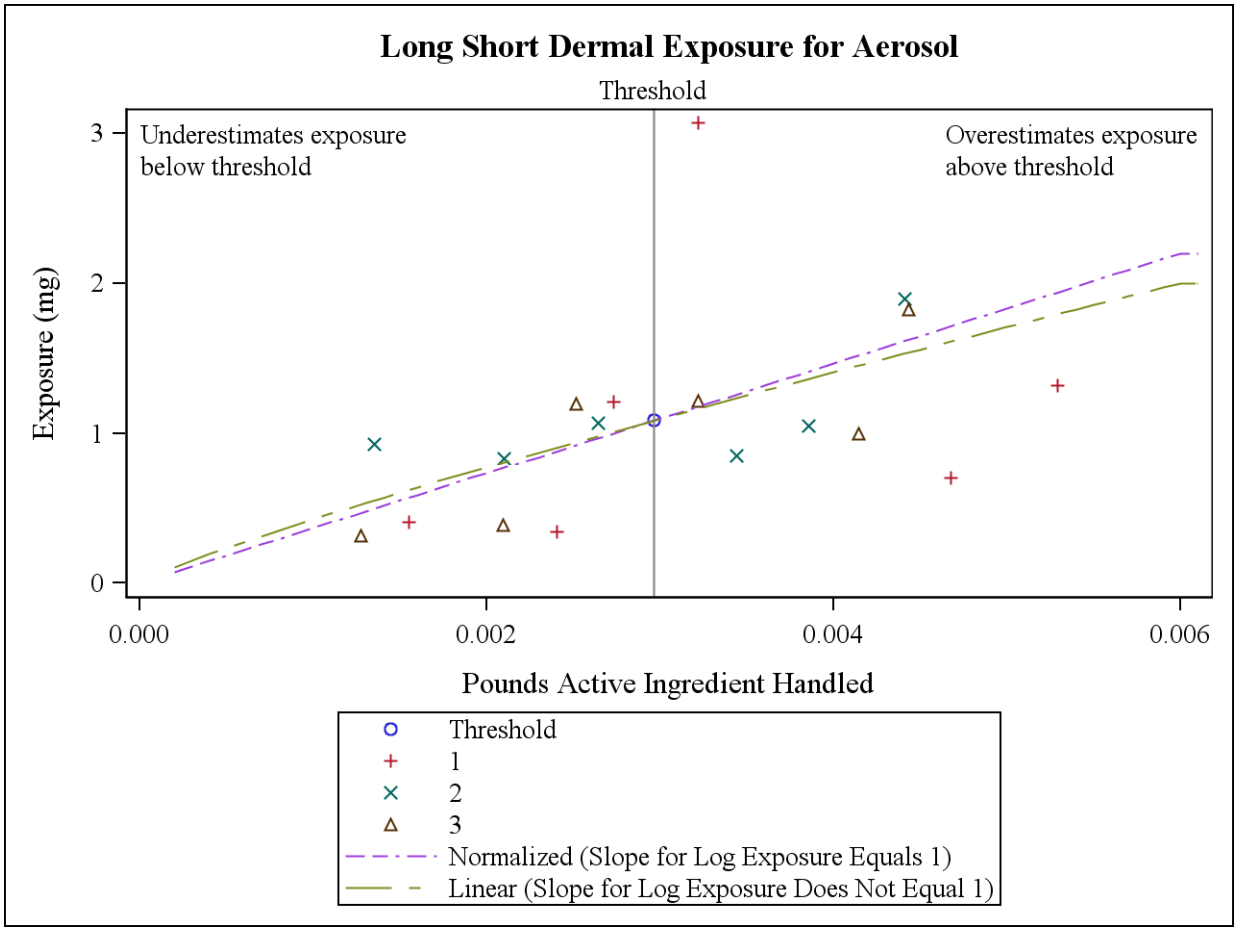
Long Short Dermal Exposure for Aerosol
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
Exposure (mg)
3
2
1
0
0.000
0.002
0.004
0.006
Pounds Active Ingredient Handled
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 32

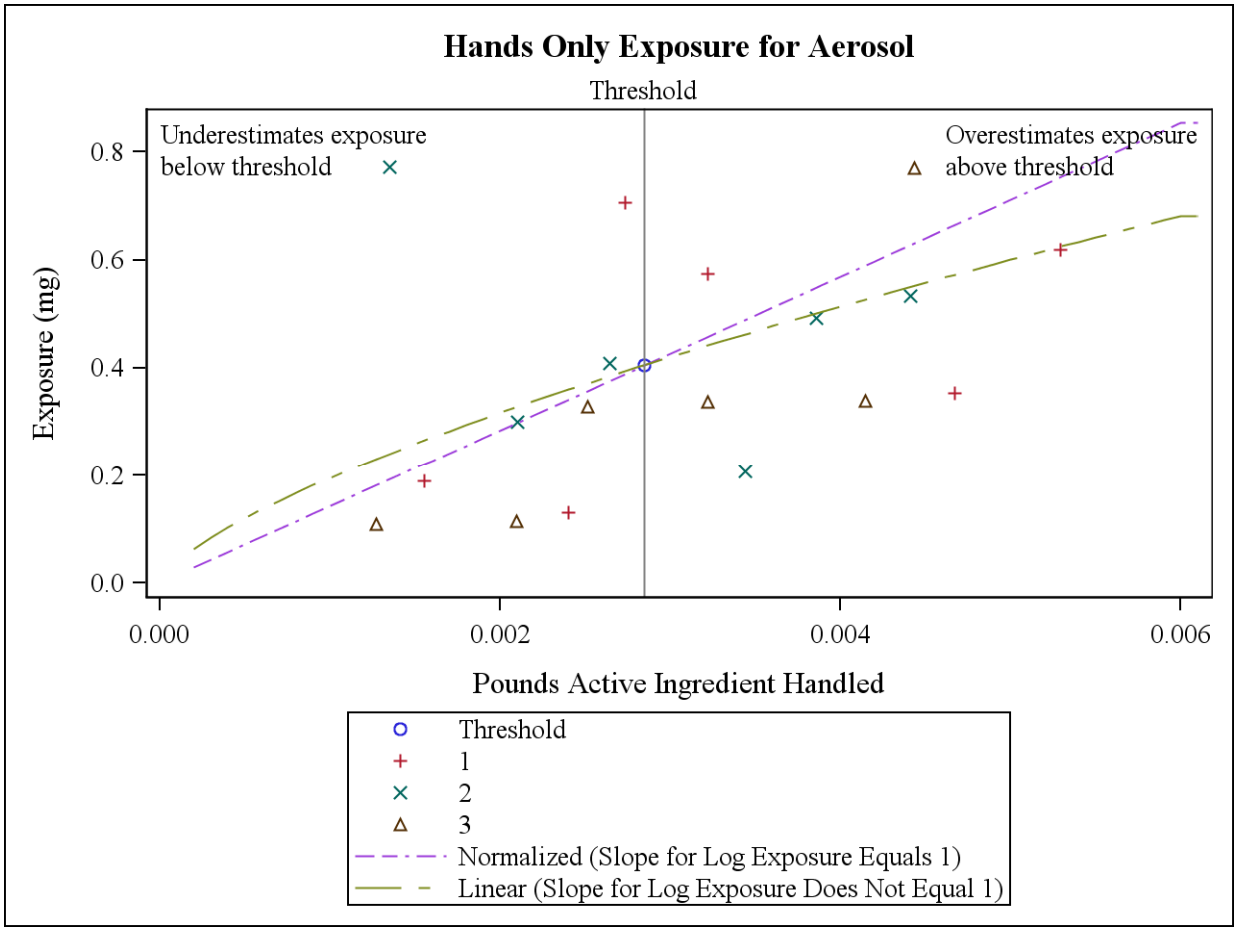
Hands Only Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0.0
0.2
0.4
0.6
0.8
0.000
0.002
0.004
0.006
Pounds Active Ingredient Handled
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 33

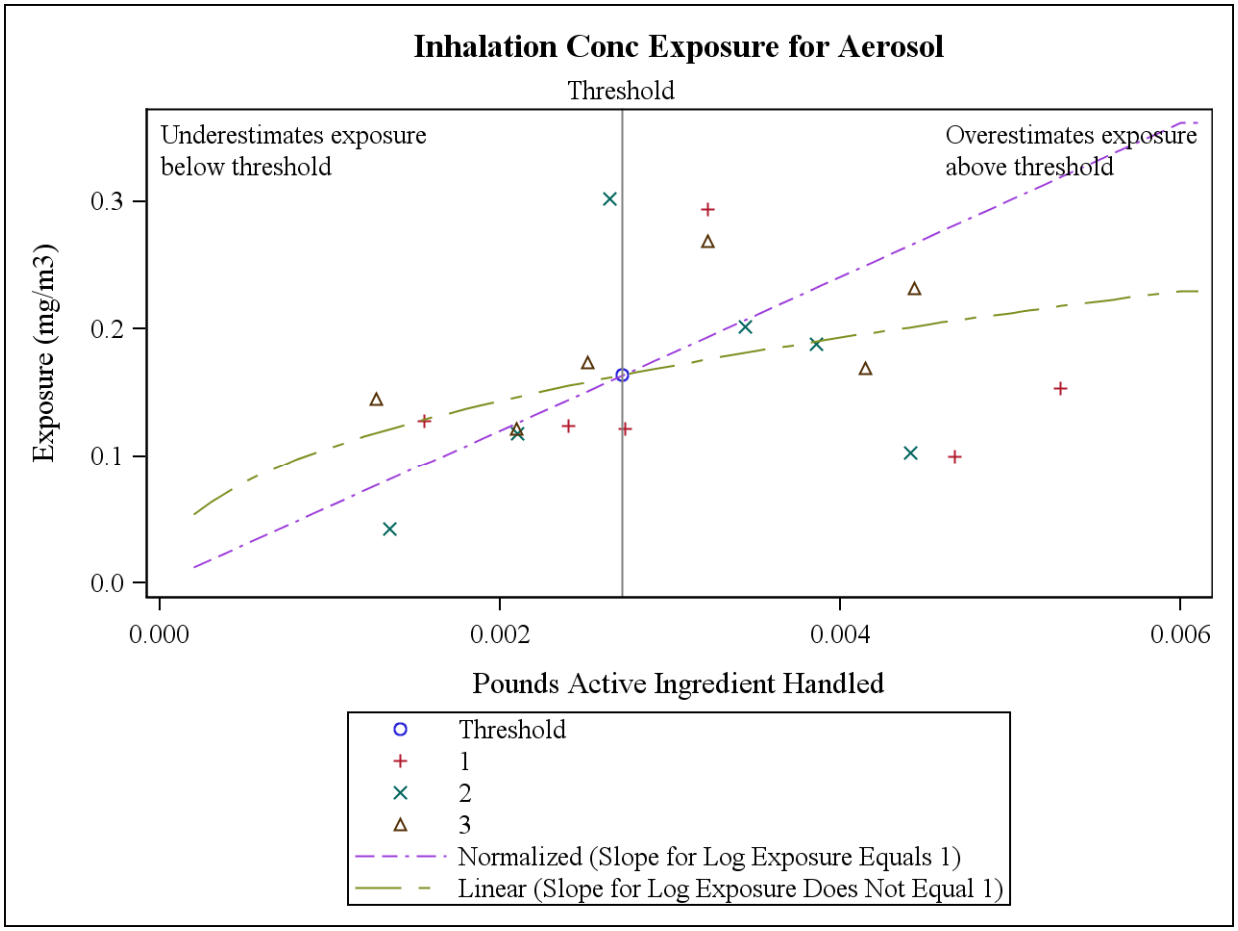

Figure 34

Alternative normalizing and exposure variables

The appendix gives the tables and graphs with the detailed results of the analysis when the exposure is normalized by the spraying duration. All the dermal exposure models are consistent with proportionality for the spraying duration. The estimated slopes for spraying duration are consistently lower than the slopes for the amount of active ingredient handled. The confidence intervals for the slopes are generally a little narrower than for the amount of active ingredient handled. The inhalation exposure models are inconsistent with proportionality for spraying duration.

The appendix also gives the tables and graphs with the detailed results of the analysis when the inhalation exposure concentration is converted to an estimated mass, calculated as the average air concentration multiplied by the spraying duration (hours) and by an estimated 1 m^3/hour of air breathed in by someone doing light activity. This value estimates the mass of C14 ADBAC breathed in by each participant. However this is an approximation because actual breathing rates are not constant and will vary with the activity as well as the individual. Moreover, the air concentration was measured and averaged over the entire air pumping period, which includes the resting periods (breaks) as well as the wiping durations. The analysis shown in the appendix is for the mass normalized by the amount of active ingredient, calculated for total inhalation and for the three particle size limits.

Using both normalizing variables (amount of active ingredient, spraying duration), the ICC value is either zero or is small (at most 0.2) for all the exposure routes, showing only a small amount of variability between the clusters, i.e., the locations including the type of food preparation area.

Finally, to compare the two different normalizing variables, we present Table 16 that gives the values of minus twice the log-likelihood "-2LL" for the alternative approaches and exposure routes. -2LL is a measure of how well a statistical model fits the data and this can be used to compare different models for the same data. (-2LL is a relative measure that can only be used to compare different models for the same data, such as the various models for the 18 long dermal exposure values. -2LL cannot be used to compare different data such as the long dermal and short dermal exposure). Using this measure, the models with the lowest -2LL values are preferred, and the preferred models in each row are shown in bold in Table 16. The values in Table 16 are -2LL for each of the mixed and repeated measures models. The log-likelihood values were computed by fitting the models using the maximum likelihood method. The rows where the slope is 1 give the -2LL values for the models where the regression slope is set to be 1 so the exposure is normalized by dividing the exposure by the normalizing variable. The rows where the slope = "Any" give the -2LL values for the more general models where the regression slope is arbitrary so the exposure is normalized by dividing the exposure by some power of the normalizing variable, NRM^p. The mixed models using the pounds of active ingredient are the preferred models for all the exposure routes except for the hands only model with an unknown slope.

Table 16. Minus twice the log-likelihood for different mixed models (smaller is better). Preferred model is shown in bold.

Exposure Route	Model	Slope	Normalized by pounds of active ingredient	Normalized by spraying duration
Long Dermal	Mixed	Any	**30.9**	31.8
	Mixed	1	**31.2**	33.8
Short Dermal	Mixed	Any	**19.6**	25.0
	Mixed	1	**19.6**	26.6
Long Short Dermal	Mixed	Any	**24.7**	27.2
	Mixed	1	**24.9**	29.8

Exposure Route	Model	Slope	Normalized by pounds of active ingredient	Normalized by spraying duration
Hands Only	Mixed	Any	29.3	**28.4**
		1	**30.2**	30.7
Dermal	Repeated Measures	Any	**-34.2**	-26.0
		1	**-33.0**	-25.6
Inhalation Concentration (mg/m^3)	Mixed	Any	**19.9**	21.7
	Mixed	1	**24.9**	32.0

APPENDIX

Analyses of exposure per spraying duration (hours)

Table and Figure Numbers are consistent with the main text (add "b").

Table 1b. Summary statistics for normalized dermal exposure.

Statistic	Normalized Long[a] Dermal (mg/hour)	Normalized Short[b] Dermal (mg/hour)	Normalized Long Short[c] Dermal (mg/hour)	Normalized Hands Only (mg/hour)
Arithmetic Mean	1.73	4.57	2.54	0.98
Arithmetic Standard Deviation	1.31	1.99	1.42	0.75
Geometric Mean	1.41	4.07	2.19	0.82
Geometric Standard Deviation	1.89	1.69	1.77	1.79
Min	0.44	1.25	0.71	0.27
5%	0.44	1.25	0.71	0.27
10%	0.63	1.90	0.98	0.44
25%	0.96	2.85	1.43	0.50
50%	1.40	5.04	2.35	0.77
75%	1.95	6.02	3.24	1.16
90%	3.85	7.00	4.38	1.68
95%	5.87	8.15	6.59	3.63
Max	5.87	8.15	6.59	3.63

[a]Long = Long pants and long sleeves
[b]Short = Short pants and short sleeves
[c]Long Short = Long pants and short sleeves

Table 2b. Summary statistics for normalized inhalation exposure.

Statistic	Normalized Inhalation (mg/m^3/hour)
Arithmetic Mean	0.42
Arithmetic Standard Deviation	0.24
Geometric Mean	0.36
Geometric Standard Deviation	1.84
Min	0.12
5%	0.12
10%	0.14
25%	0.26
50%	0.39
75%	0.53
90%	0.88
95%	0.93
Max	0.93

Table 3b. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Dermal (mg/hour)	Long pants and long sleeves	1.72 (1.25, 2.42)	4.01 (2.53, 6.34)
	Short pants and short sleeves	4.72 (3.23, 6.99)	9.96 (6.02, 16.42)
	Long pants and short sleeves	2.58 (1.90, 3.57)	5.62 (3.62, 8.69)
	Hands only	0.97 (0.72, 1.31)	2.13 (1.40, 3.25)
Inhalation (mg/m^3/hour)		0.44 (0.29, 0.67)	1.01 (0.58, 1.75)

Table 4b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.89	1.53	2.34	1.24	1.54	2.16	1.23
GSDm	1.89	1.54	2.36	1.25	1.57	2.20	1.21

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
ICC	0.00	0.00	0.39		0.00	0.76	
GMs	1.41	1.05	1.90	1.35	1.10	1.88	1.33
GMm	1.41	1.05	1.90	1.35	1.10	1.88	1.33
AMs	1.73	1.24	2.37	1.40	1.23	2.36	1.40
AMu	1.72	1.25	2.41	1.39	1.25	2.39	1.38
AMm	1.72	1.25	2.42	1.40	1.28	2.40	1.39
P95s	5.87	2.52	9.31	2.34	2.16	5.87	2.72
P95u	4.01	2.51	6.25	1.60	2.42	6.04	1.66
P95m	4.01	2.53	6.34	1.59	2.54	6.12	1.58

Table 5b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized short dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.69	1.41	2.05	1.21	1.48	1.88	1.14
GSDm	1.72	1.42	2.15	1.25	1.48	2.01	1.16
ICC	0.21	0.00	0.66		0.00	0.84	
GMs	4.07	2.84	5.89	1.45	3.35	5.01	1.23
GMm	4.07	2.84	5.89	1.45	3.35	5.01	1.23
AMs	4.57	3.19	6.77	1.48	3.78	5.42	1.21
AMu	4.68	3.21	6.85	1.46	3.84	5.56	1.22
AMm	4.72	3.23	6.99	1.48	3.94	5.57	1.20
P95s	8.15	5.96	20.77	2.55	6.31	8.15	1.29
P95u	9.69	5.96	15.55	1.63	7.57	11.57	1.28
P95m	9.96	6.02	16.42	1.66	7.92	12.28	1.26

Table 6b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long short dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.77	1.47	2.13	1.21	1.52	1.95	1.16
GSDm	1.77	1.47	2.16	1.22	1.54	2.01	1.15
ICC	0.04	0.00	0.46		0.00	0.80	
GMs	2.19	1.64	2.95	1.35	1.76	2.79	1.28
GMm	2.19	1.64	2.95	1.35	1.76	2.79	1.28
AMs	2.54	1.87	3.51	1.38	1.98	3.21	1.28
AMu	2.58	1.89	3.55	1.38	2.00	3.28	1.29
AMm	2.58	1.90	3.57	1.38	2.05	3.28	1.27
P95s	6.59	3.59	12.20	1.85	3.27	6.59	2.01
P95u	5.59	3.59	8.52	1.56	3.93	7.37	1.42
P95m	5.62	3.62	8.69	1.55	4.12	7.46	1.37

Table 7b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized hands only exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.79	1.48	2.18	1.22	1.43	2.17	1.25
GSDm	1.79	1.49	2.20	1.23	1.44	2.27	1.26
ICC	0.00	0.00	0.39		0.00	0.59	
GMs	0.82	0.62	1.07	1.32	0.64	1.06	1.30
GMm	0.82	0.62	1.07	1.32	0.64	1.06	1.30
AMs	0.98	0.72	1.29	1.37	0.71	1.34	1.38
AMu	0.97	0.72	1.31	1.35	0.71	1.34	1.38
AMm	0.97	0.72	1.31	1.36	0.72	1.37	1.41
P95s	3.63	1.39	4.62	2.61	1.19	3.63	3.05
P95u	2.13	1.39	3.21	1.54	1.29	3.40	1.66
P95m	2.13	1.40	3.25	1.53	1.31	3.64	1.70

Table 8b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.84	1.50	2.28	1.24	1.54	2.10	1.20
GSDm	1.87	1.50	2.38	1.28	1.55	2.23	1.21
ICC	0.17	0.00	0.62		0.00	0.66	
GMs	0.36	0.24	0.54	1.50	0.28	0.46	1.27
GMm	0.36	0.24	0.54	1.50	0.28	0.46	1.27
AMs	0.42	0.28	0.65	1.53	0.33	0.53	1.28
AMu	0.43	0.29	0.66	1.52	0.34	0.55	1.29
AMm	0.44	0.29	0.67	1.54	0.34	0.56	1.28
P95s	0.93	0.58	2.35	2.52	0.63	0.93	1.47
P95u	0.98	0.57	1.66	1.71	0.68	1.30	1.44
P95m	1.01	0.58	1.75	1.74	0.71	1.39	1.42

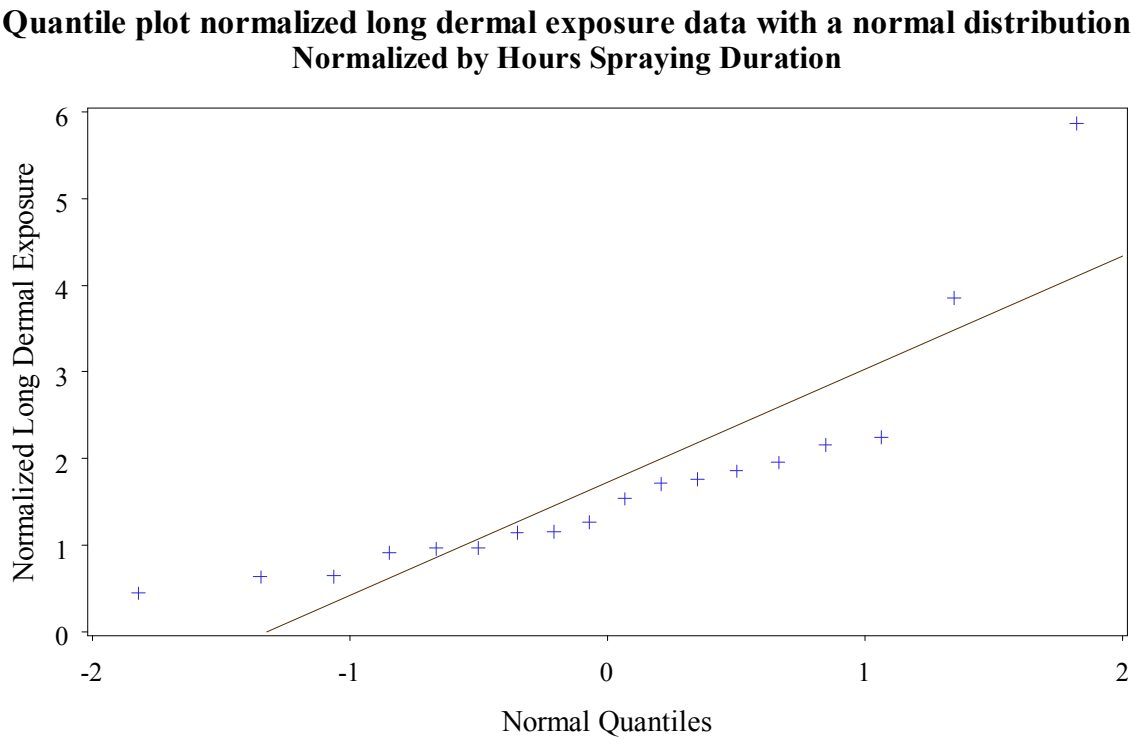
Quantile plot normalized long dermal exposure data with a normal distribution
Normalized by Hours Spraying Duration
Normalized Long Dermal Exposure
0
1
2
3
4
5
6
-2
-1
0
1
2
Normal Quantiles

Figure 1b

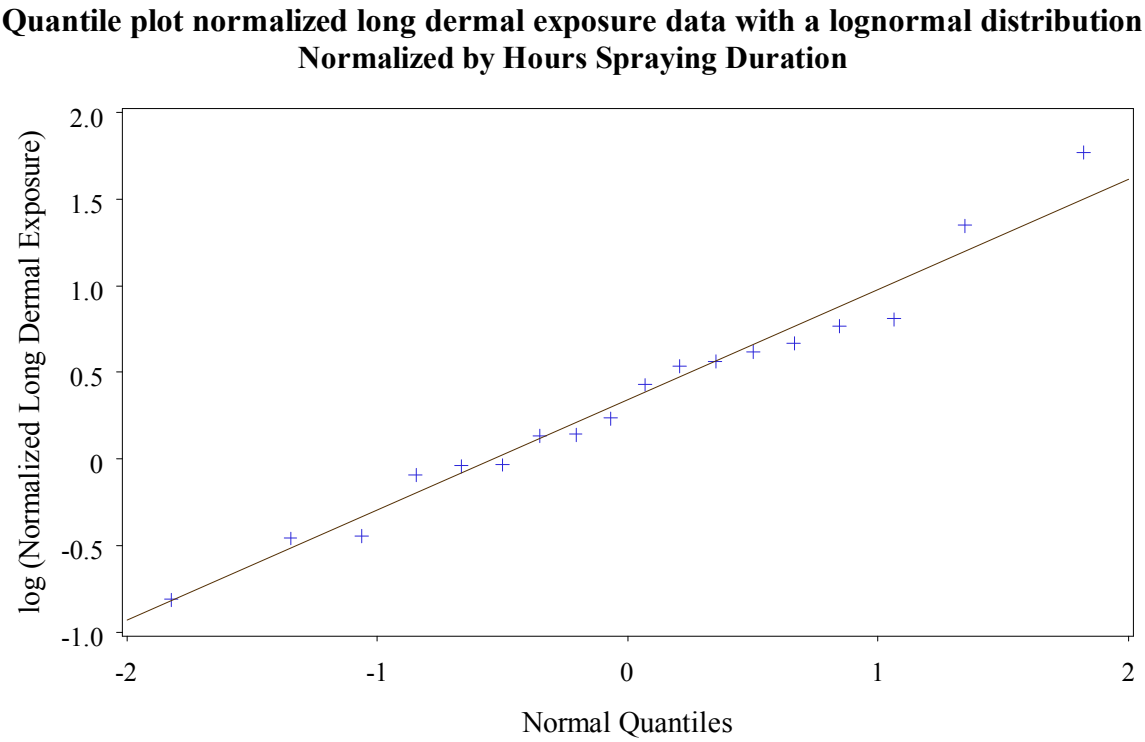
Quantile plot normalized long dermal exposure data with a lognormal distribution
Normalized by Hours Spraying Duration
log (Normalized Long Dermal Exposure)
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-2
-1
0
1
2
Normal Quantiles

Figure 2b

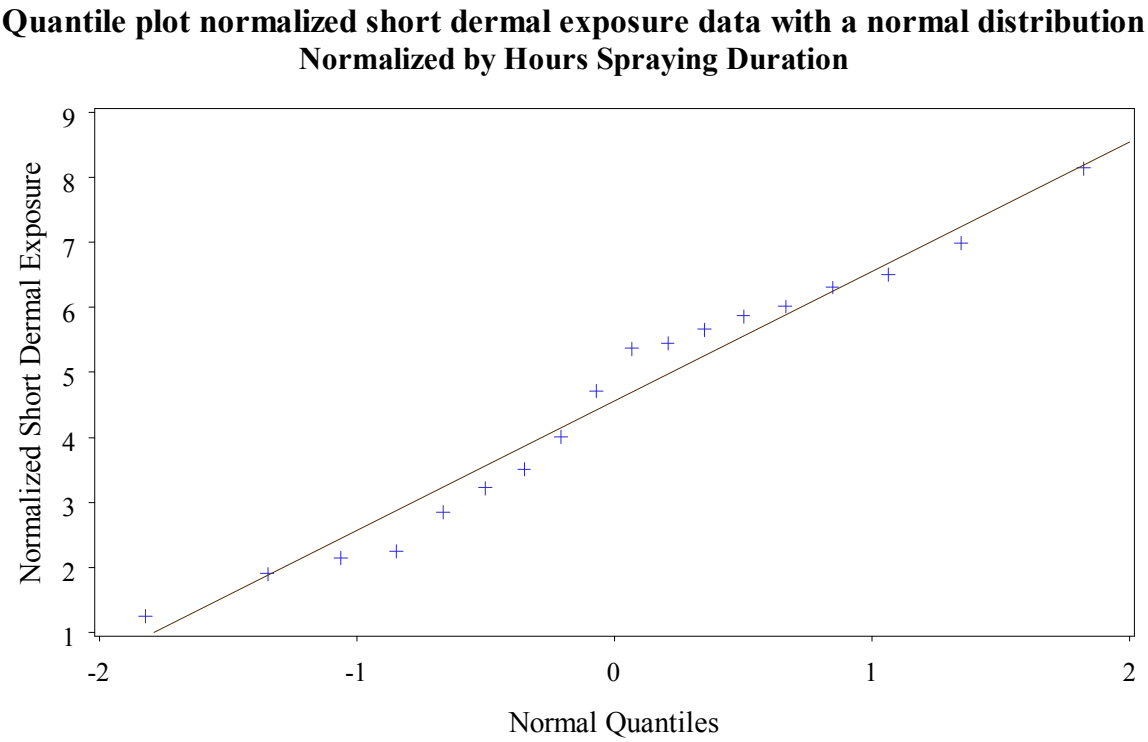
Quantile plot normalized short dermal exposure data with a normal distribution
Normalized by Hours Spraying Duration
Normalized Short Dermal Exposure
9
8
7
6
5
4
3
2
1
-2
-1
0
1
2
Normal Quantiles

Figure 3b

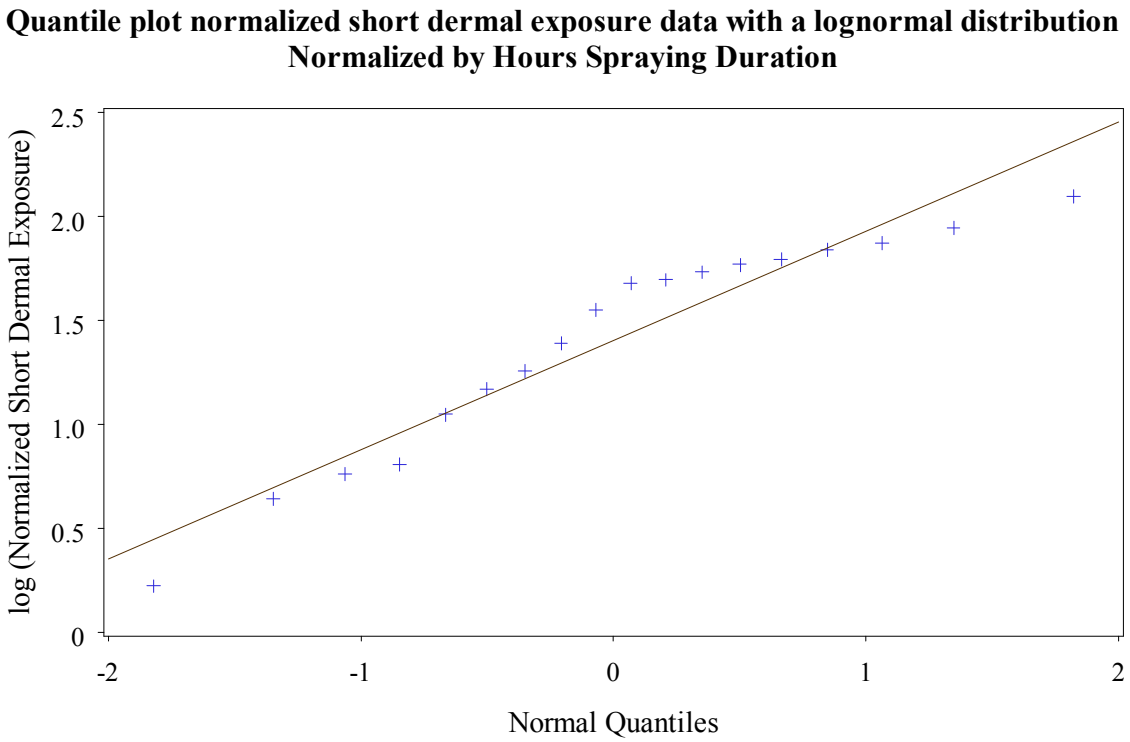
Quantile plot normalized short dermal exposure data with a lognormal distribution
Normalized by Hours Spraying Duration
log (Normalized Short Dermal Exposure)
2.5
2.0
1.5
1.0
0.5
0
-2
-1
0
1
2
Normal Quantiles

Figure 4b

Quantile plot normalized long short dermal exposure data with a normal distribution
Normalized by Hours Spraying Duration

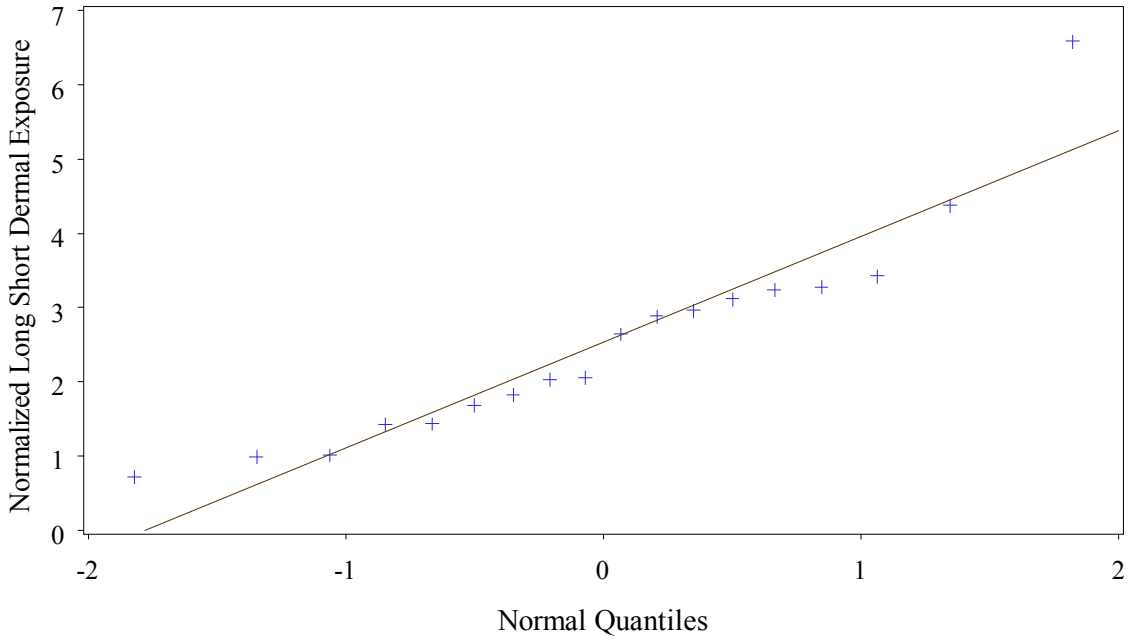

Figure 5b

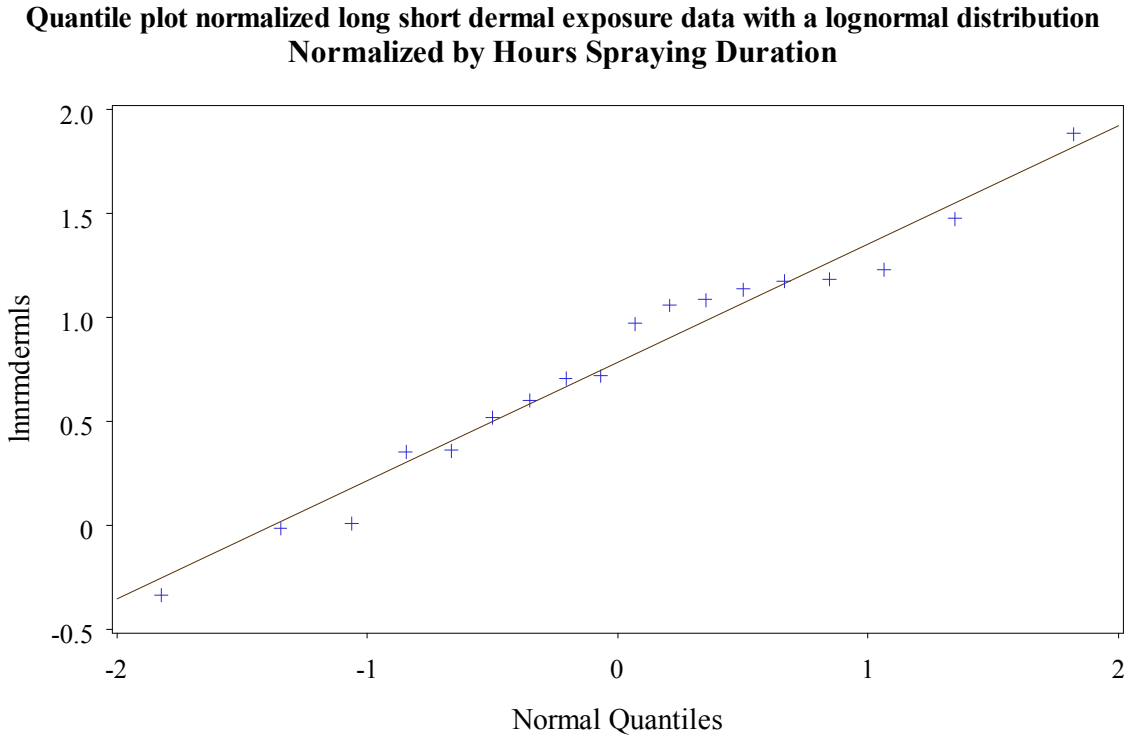
Quantile plot normalized long short dermal exposure data with a lognormal distribution
Normalized by Hours Spraying Duration
lnnrmdermls
2.0
1.5
1.0
0.5
0
-0.5
-2
-1
0
1
2
Normal Quantiles

Figure 6b

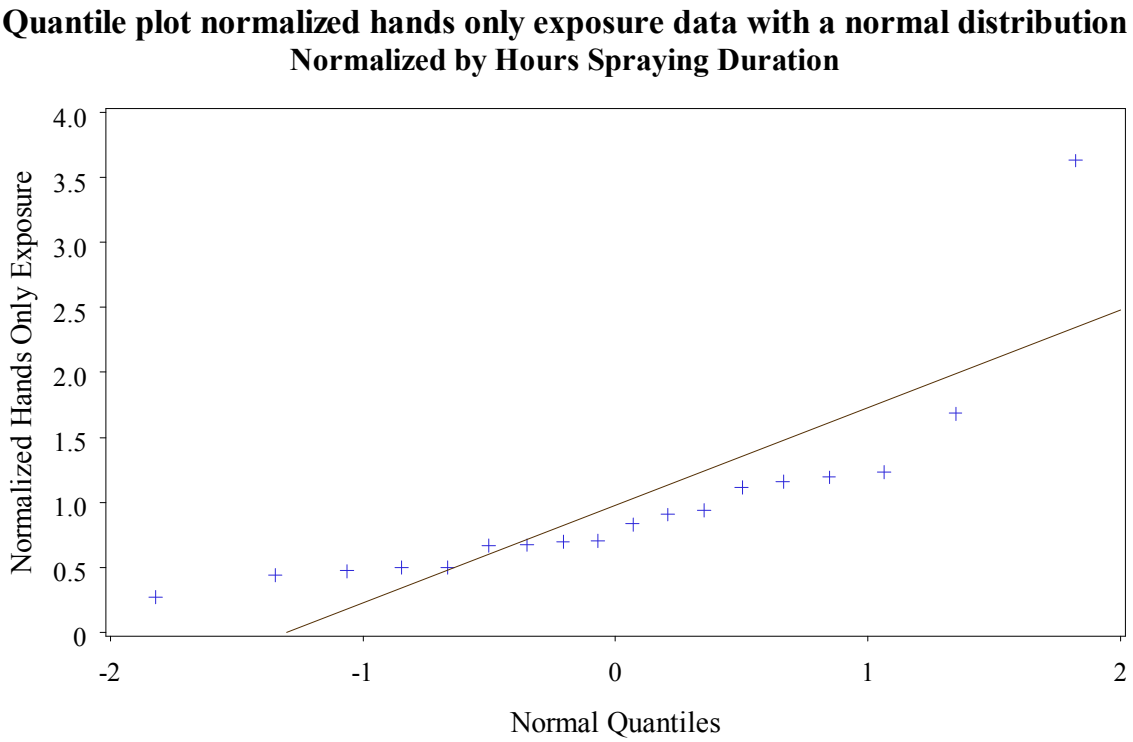
Quantile plot normalized hands only exposure data with a normal distribution
Normalized by Hours Spraying Duration
Normalized Hands Only Exposure
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-2
-1
0
1
2
Normal Quantiles

Figure 7b

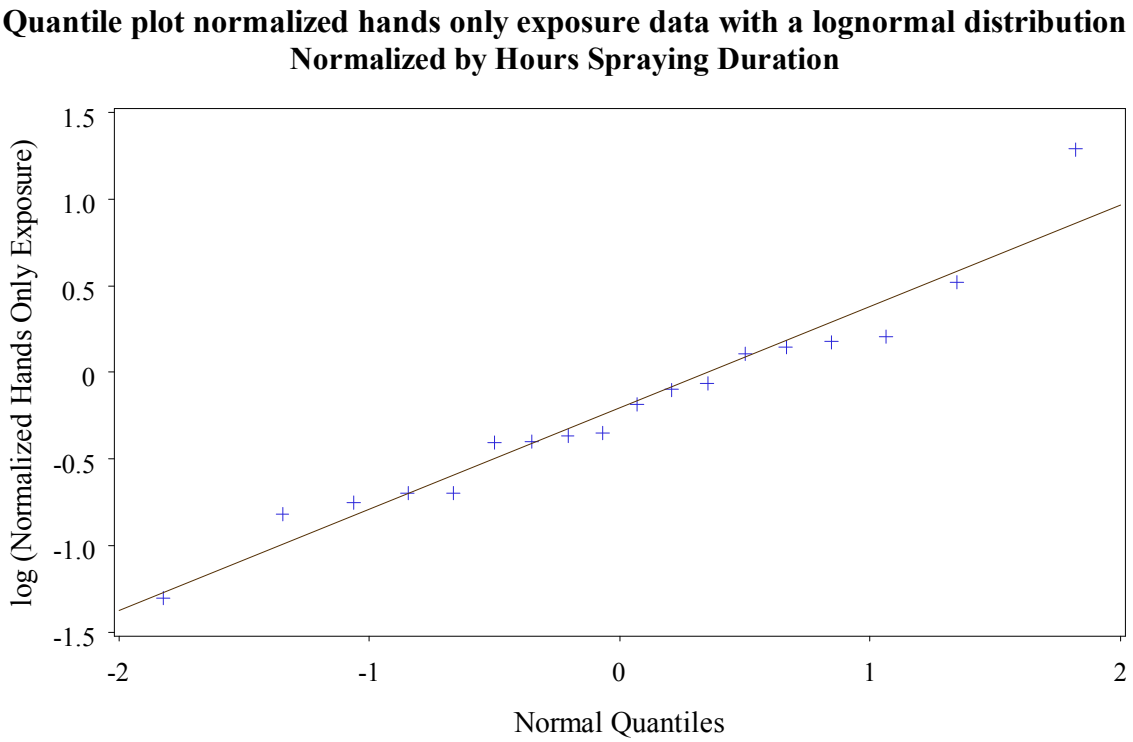
Quantile plot normalized hands only exposure data with a lognormal distribution
Normalized by Hours Spraying Duration
log (Normalized Hands Only Exposure)
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2
-1
0
1
2
Normal Quantiles

Figure 8b

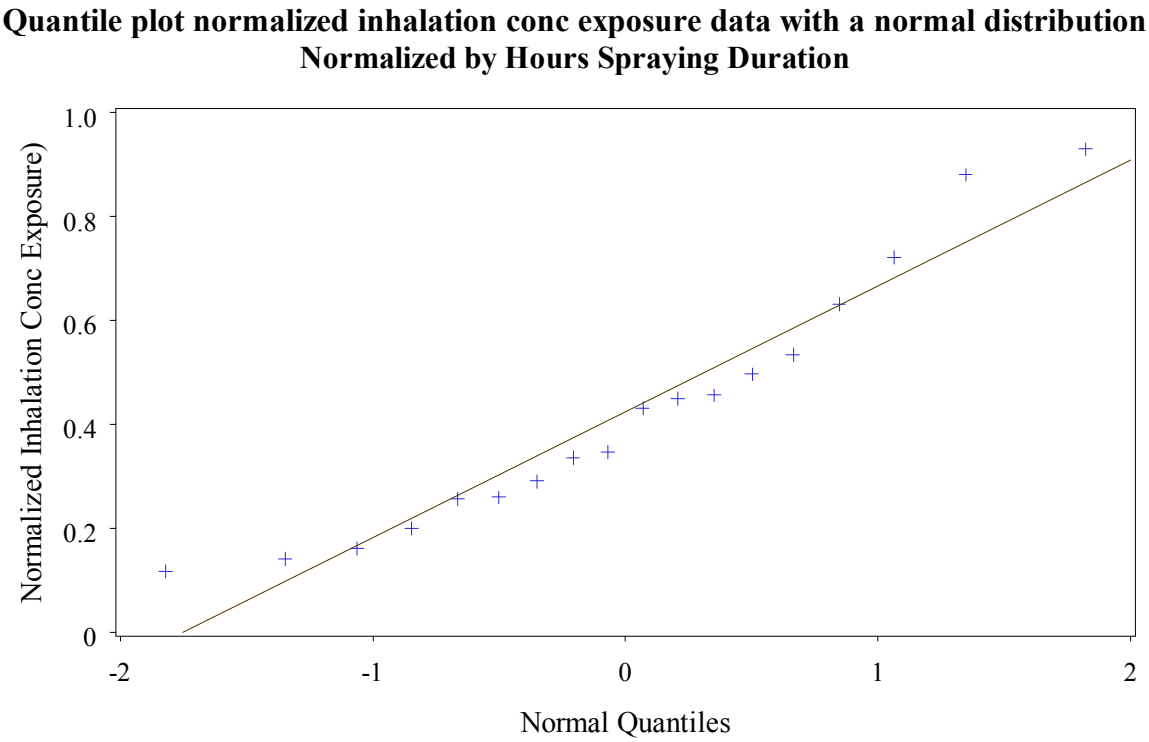
Quantile plot normalized inhalation conc exposure data with a normal distribution
Normalized by Hours Spraying Duration
Normalized Inhalation Conc Exposure)
1.0
0.8
0.6
0.4
0.2
0
-2
-1
0
1
2
Normal Quantiles

Figure 9b

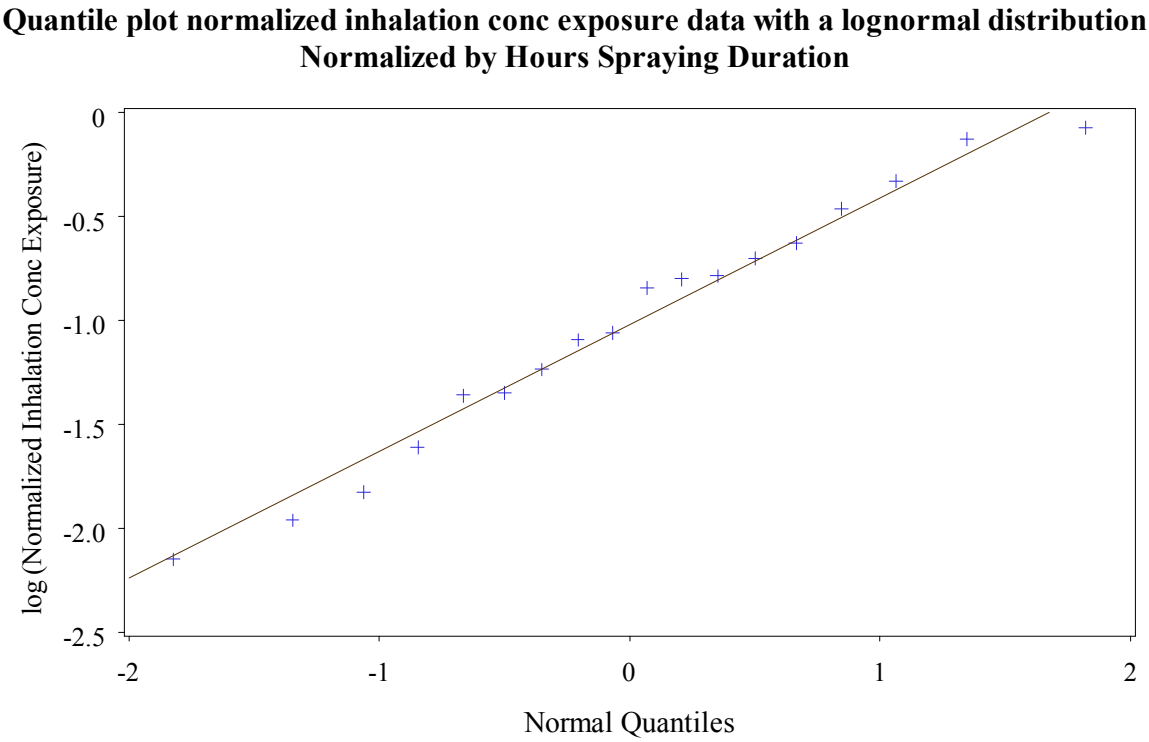
Quantile plot normalized inhalation conc exposure data with a lognormal distribution
Normalized by Hours Spraying Duration
log (Normalized Inhalation Conc Exposure)
0
-0.5
-1.0
-1.5
-2.0
-2.5
-2
-1
0
1
2
Normal Quantiles

Figure 10b

Table 13b. 95 percent confidence intervals for the slope of log exposure versus log spraying duration.

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	Mixed	0.61	-0.01	1.22	1.23
		Simple Linear	0.61	-0.00	1.22	1.22
	Short pants and short sleeves	Mixed	0.73	0.19	1.28	1.10
		Simple Linear	0.67	0.17	1.18	1.01
	Long pants and short sleeves	Mixed	0.61	0.07	1.14	1.07
		Simple Linear	0.61	0.07	1.14	1.07
	Hands Only	Mixed	0.61	0.05	1.18	1.12
		Simple Linear	0.61	0.06	1.17	1.11
	None	Mixed	0.79	0.33	1.25	0.92
		Simple Linear	0.71	0.27	1.15	0.88
Inhalation (mg/m^3)		Mixed	0.23	-0.30	0.76	1.06
		Simple Linear	0.22	-0.24	0.68	0.92
Dermal (mg)	Any	Repeated Measures	0.91	0.36	1.45	1.09

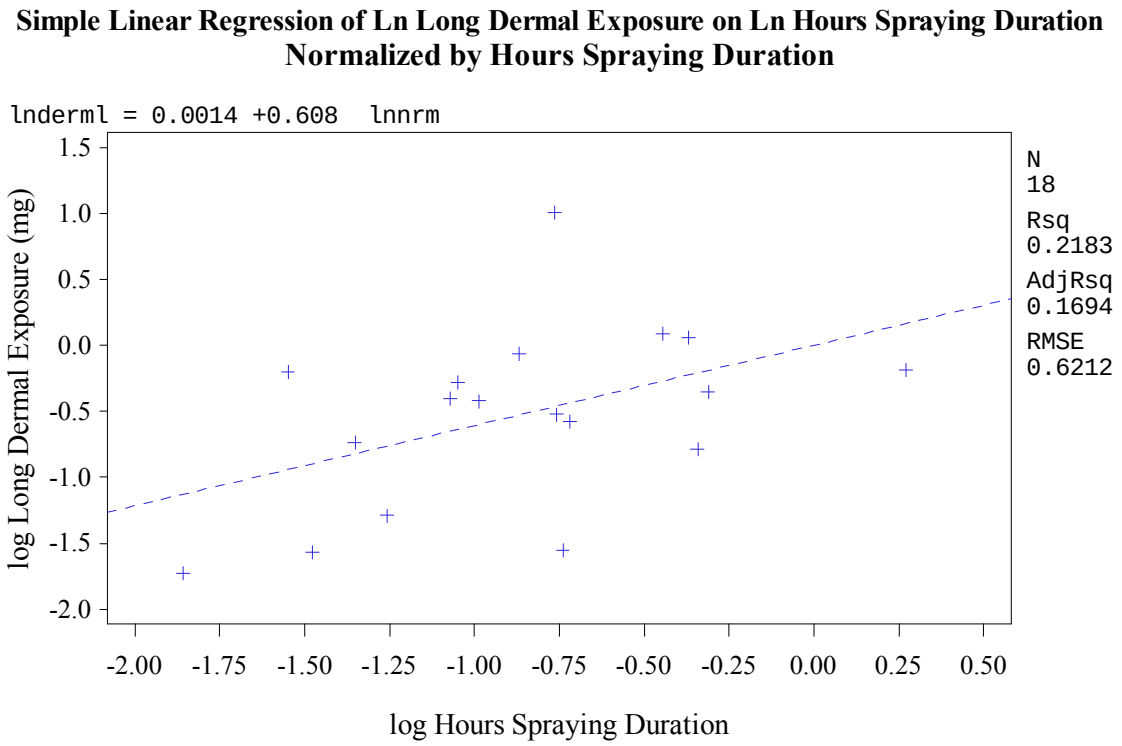
Simple Linear Regression of Ln Long Dermal Exposure on Ln Hours Spraying Duration
Normalized by Hours Spraying Duration
lnderml = 0.0014 +0.608 lnnrm
N
18
Rsq
0.2183
AdjRsq
0.1694
RMSE
0.6212
log Long Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.00
-1.75
-1.50
-1.25
-1.00
-0.75
-0.50
-0.25
0.00
0.25
0.50
log Hours Spraying Duration

Figure 17b

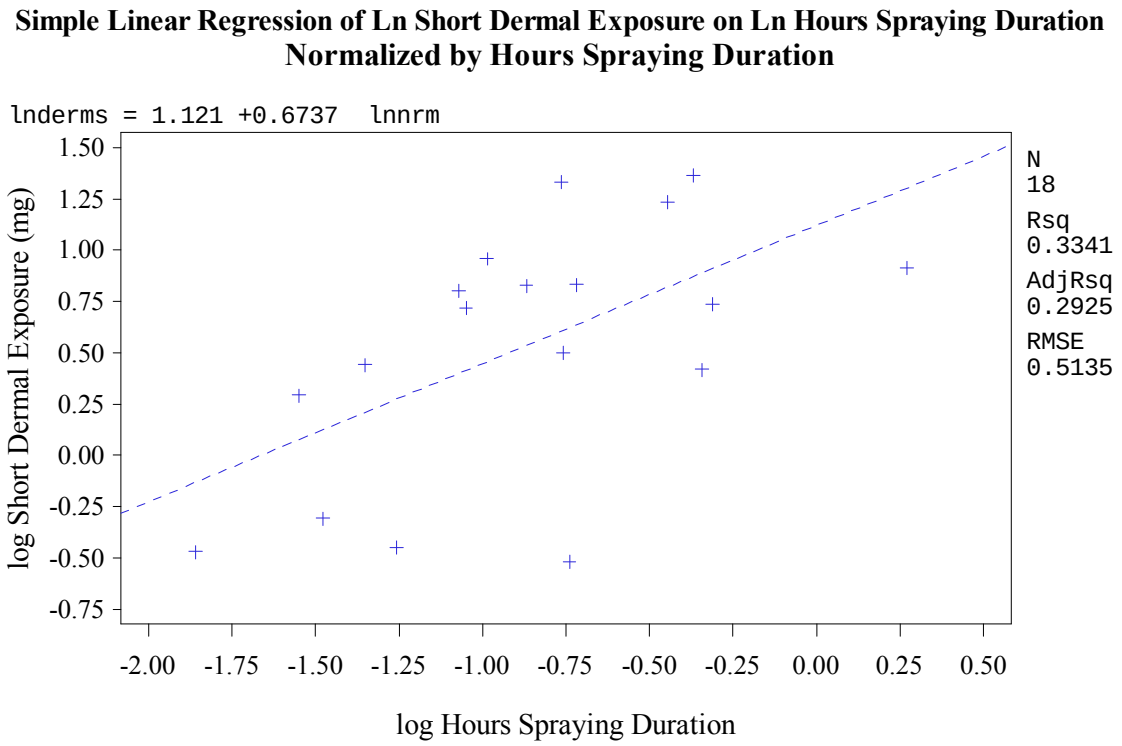
Simple Linear Regression of Ln Short Dermal Exposure on Ln Hours Spraying Duration
Normalized by Hours Spraying Duration
lnderms = 1.121 +0.6737 lnnrm
N
18
Rsq
0.3341
AdjRsq
0.2925
RMSE
0.5135
log Short Dermal Exposure (mg)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-2.00
-1.75
-1.50
-1.25
-1.00
-0.75
-0.50
-0.25
0.00
0.25
0.50
log Hours Spraying Duration

Figure 18b

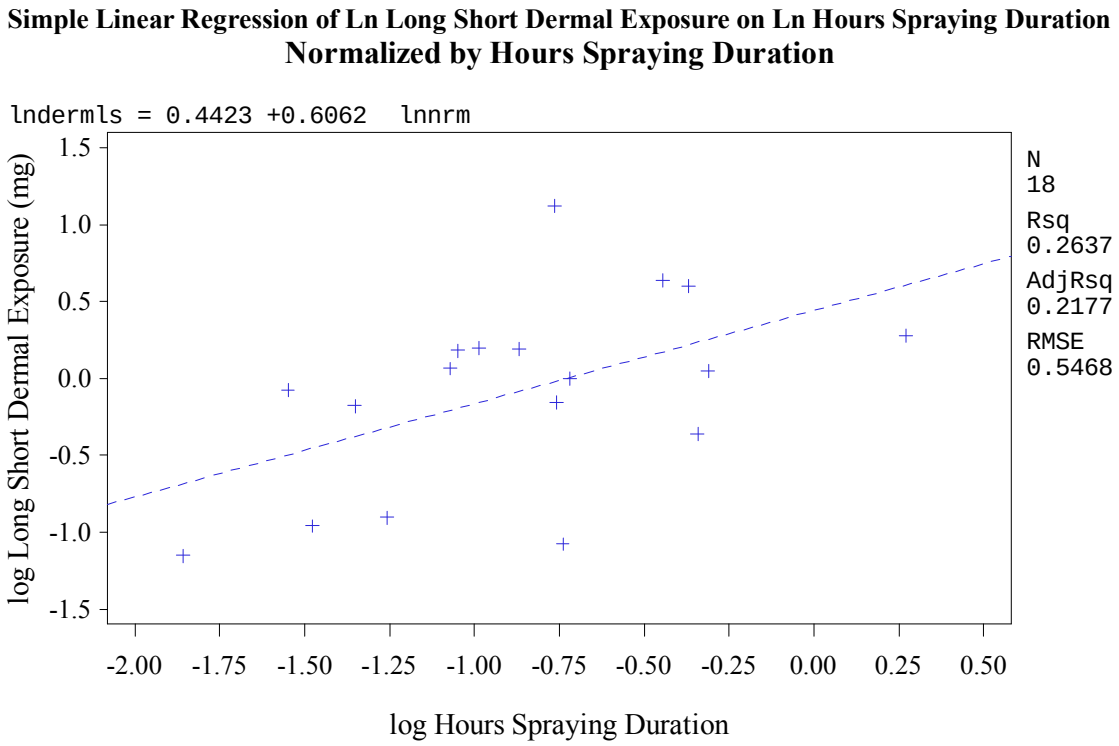
Simple Linear Regression of Ln Long Short Dermal Exposure on Ln Hours Spraying Duration
Normalized by Hours Spraying Duration
lndermls = 0.4423 +0.6062 lnnrm
log Long Short Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.00
-1.75
-1.50
-1.25
-1.00
-0.75
-0.50
-0.25
0.00
0.25
0.50
log Hours Spraying Duration
N
18
Rsq
0.2637
AdjRsq
0.2177
RMSE
0.5468

Figure 19b

Simple Linear Regression of Ln All Dermal Exposure on Ln Hours Spraying Duration Normalized by Hours Spraying Duration

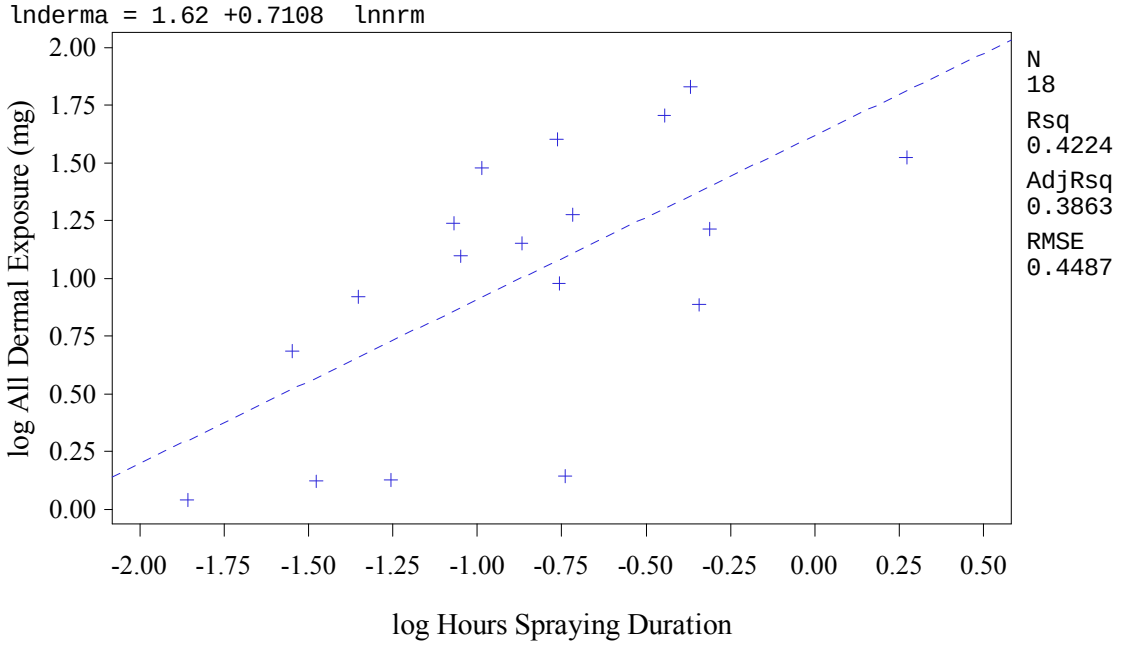

Figure 20b

Simple Linear Regression of Ln Hands Only Exposure on Ln Hours Spraying Duration Normalized by Hours Spraying Duration

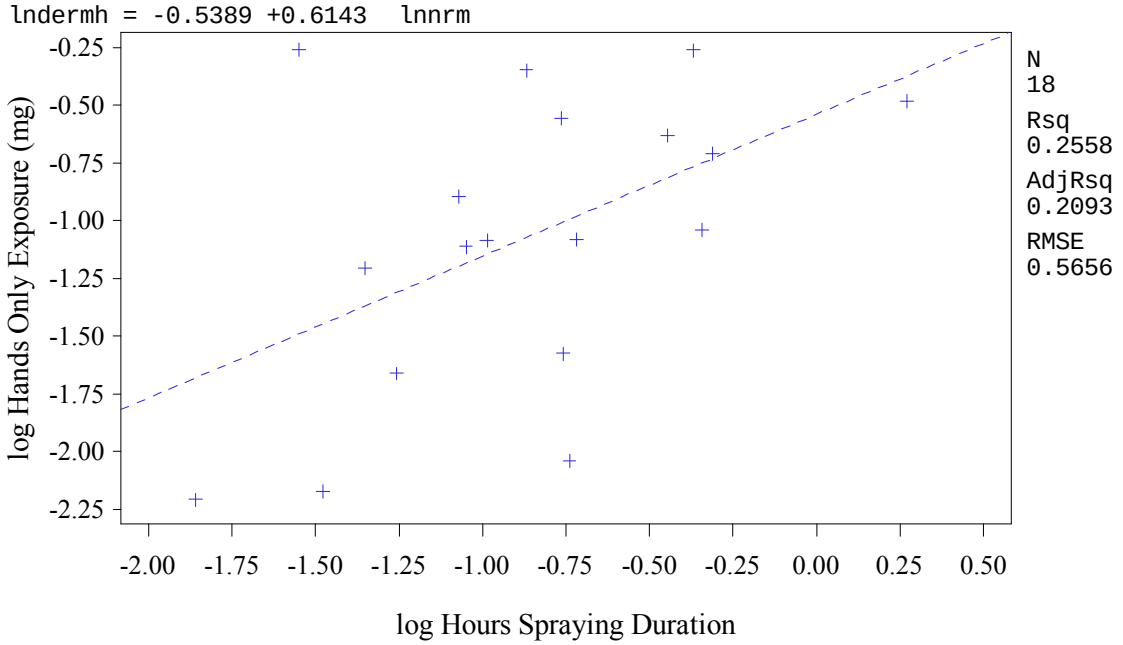

Figure 21b

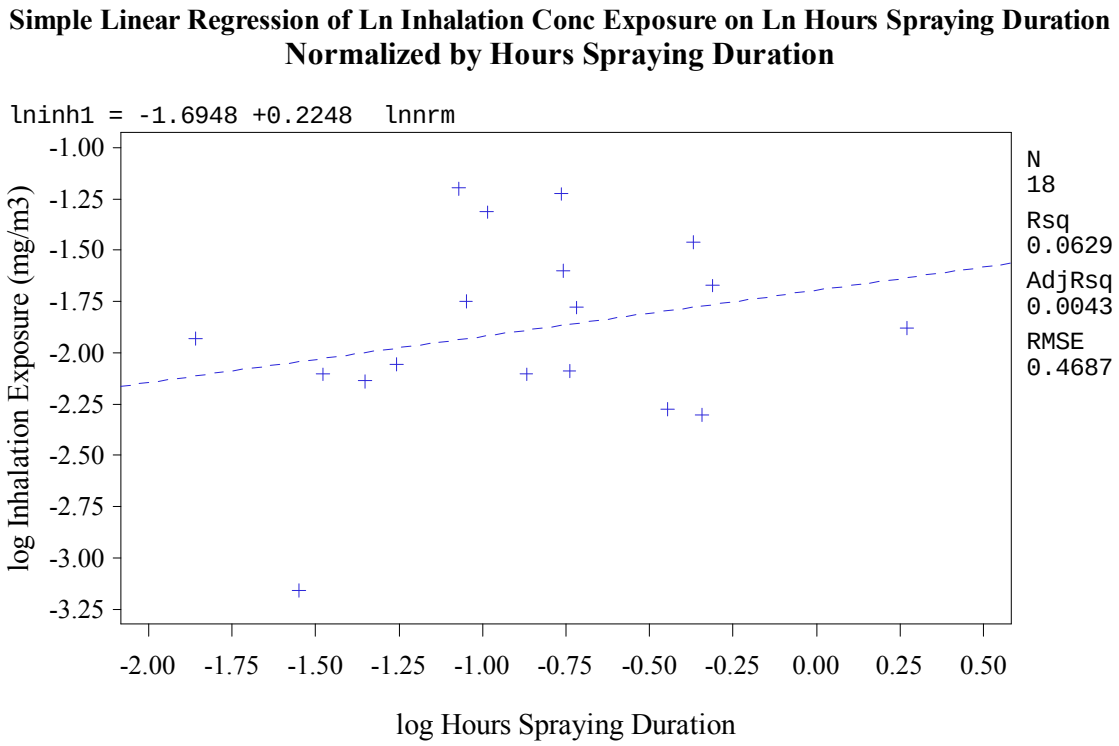
Simple Linear Regression of Ln Inhalation Conc Exposure on Ln Hours Spraying Duration
Normalized by Hours Spraying Duration
lninh1 = -1.6948 +0.2248 lnnrm
log Inhalation Exposure (mg/m3)
-1.00
-1.25
-1.50
-1.75
-2.00
-2.25
-2.50
-2.75
-3.00
-3.25
-2.00
-1.75
-1.50
-1.25
-1.00
-0.75
-0.50
-0.25
0.00
0.25
0.50
log Hours Spraying Duration
N
18
Rsq
0.0629
AdjRsq
0.0043
RMSE
0.4687

Figure 22b

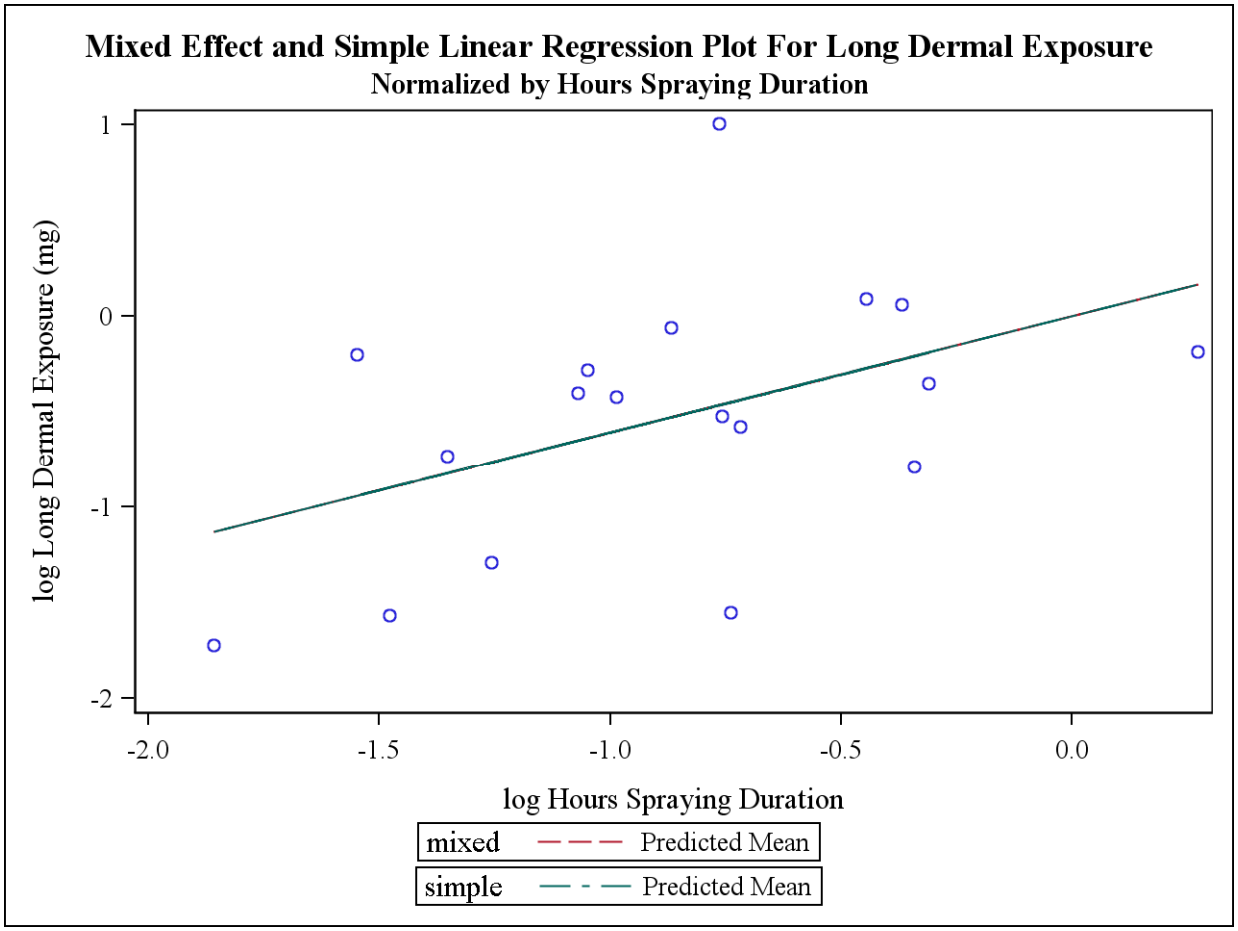
Mixed Effect and Simple Linear Regression Plot For Long Dermal Exposure
Normalized by Hours Spraying Duration
log Long Dermal Exposure (mg)
1
0
-1
-2
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed Predicted Mean
simple Predicted Mean

Figure 23b

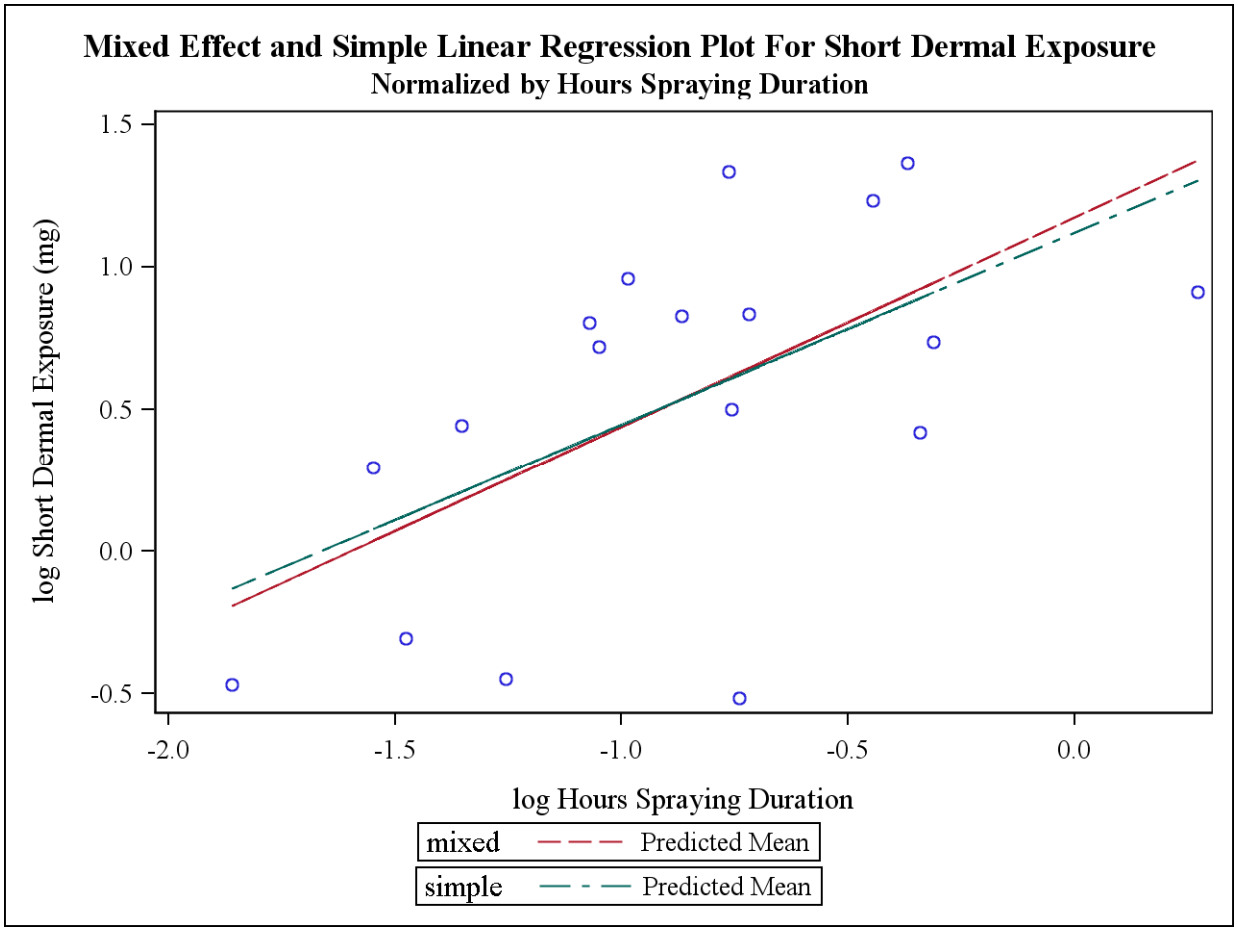
Mixed Effect and Simple Linear Regression Plot For Short Dermal Exposure
Normalized by Hours Spraying Duration
log Short Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 24b

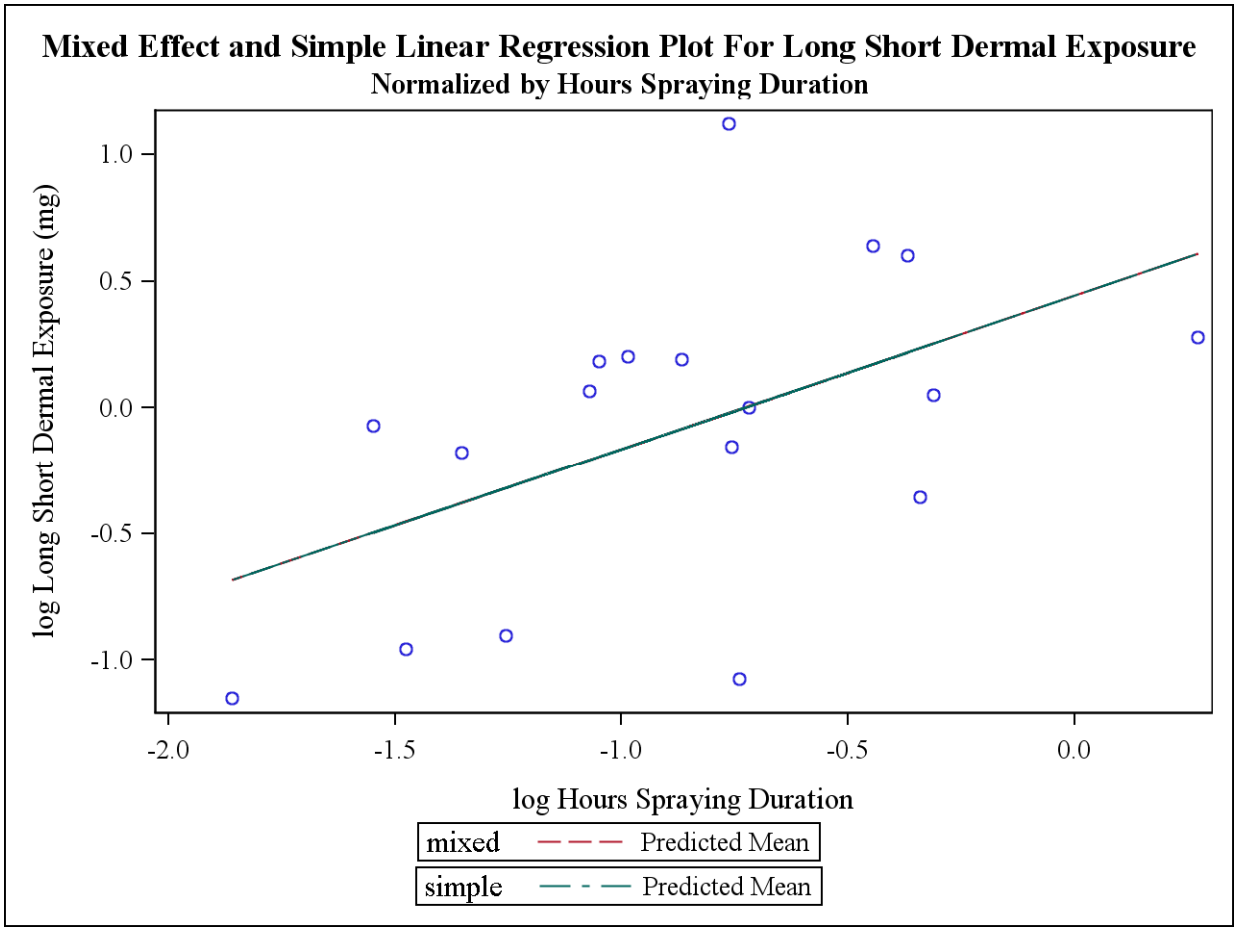
Mixed Effect and Simple Linear Regression Plot For Long Short Dermal Exposure
Normalized by Hours Spraying Duration
log Long Short Dermal Exposure (mg)
1.0
0.5
0.0
-0.5
-1.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed Predicted Mean
simple Predicted Mean

Figure 25b

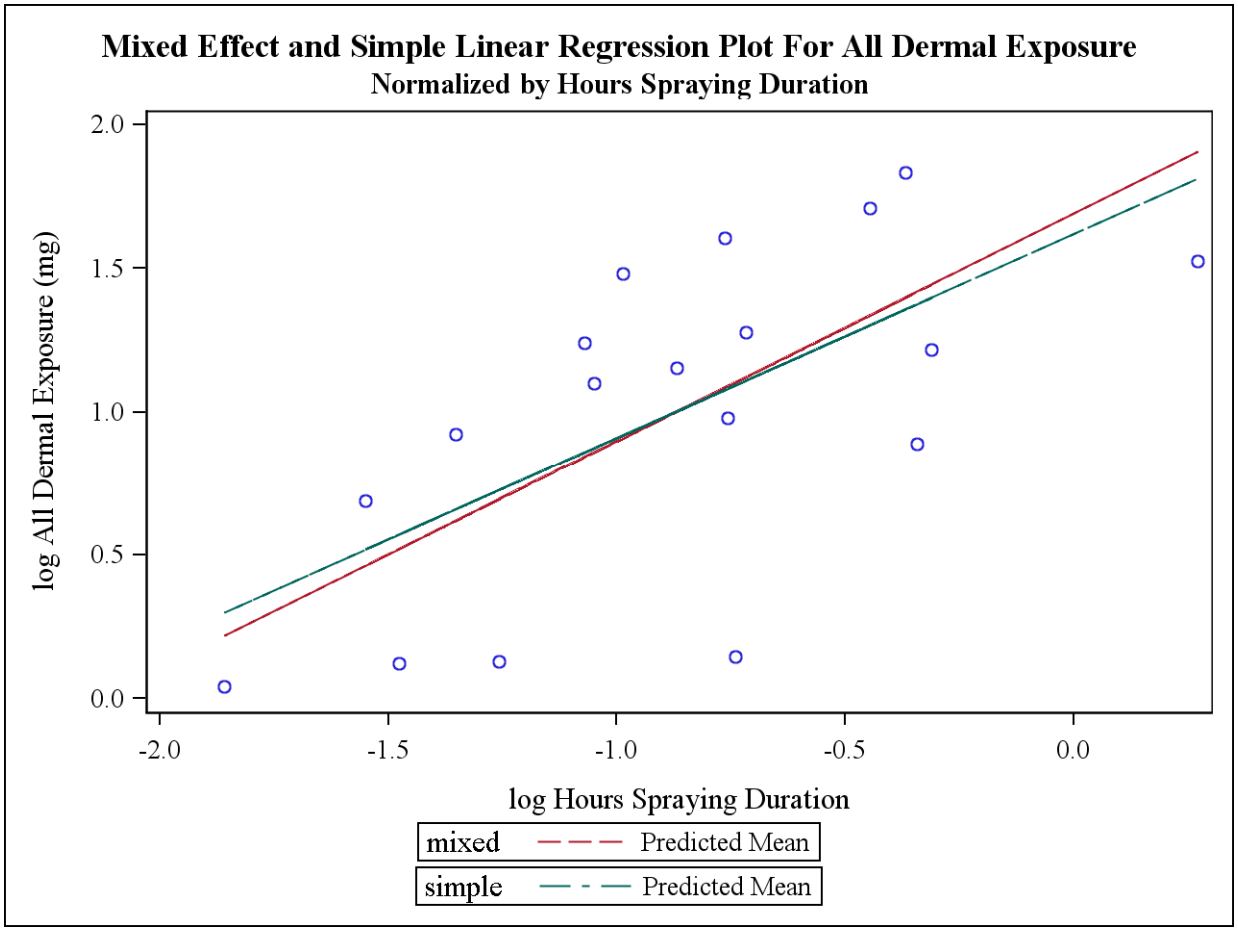
Mixed Effect and Simple Linear Regression Plot For All Dermal Exposure
Normalized by Hours Spraying Duration
log All Dermal Exposure (mg)
2.0
1.5
1.0
0.5
0.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 26b

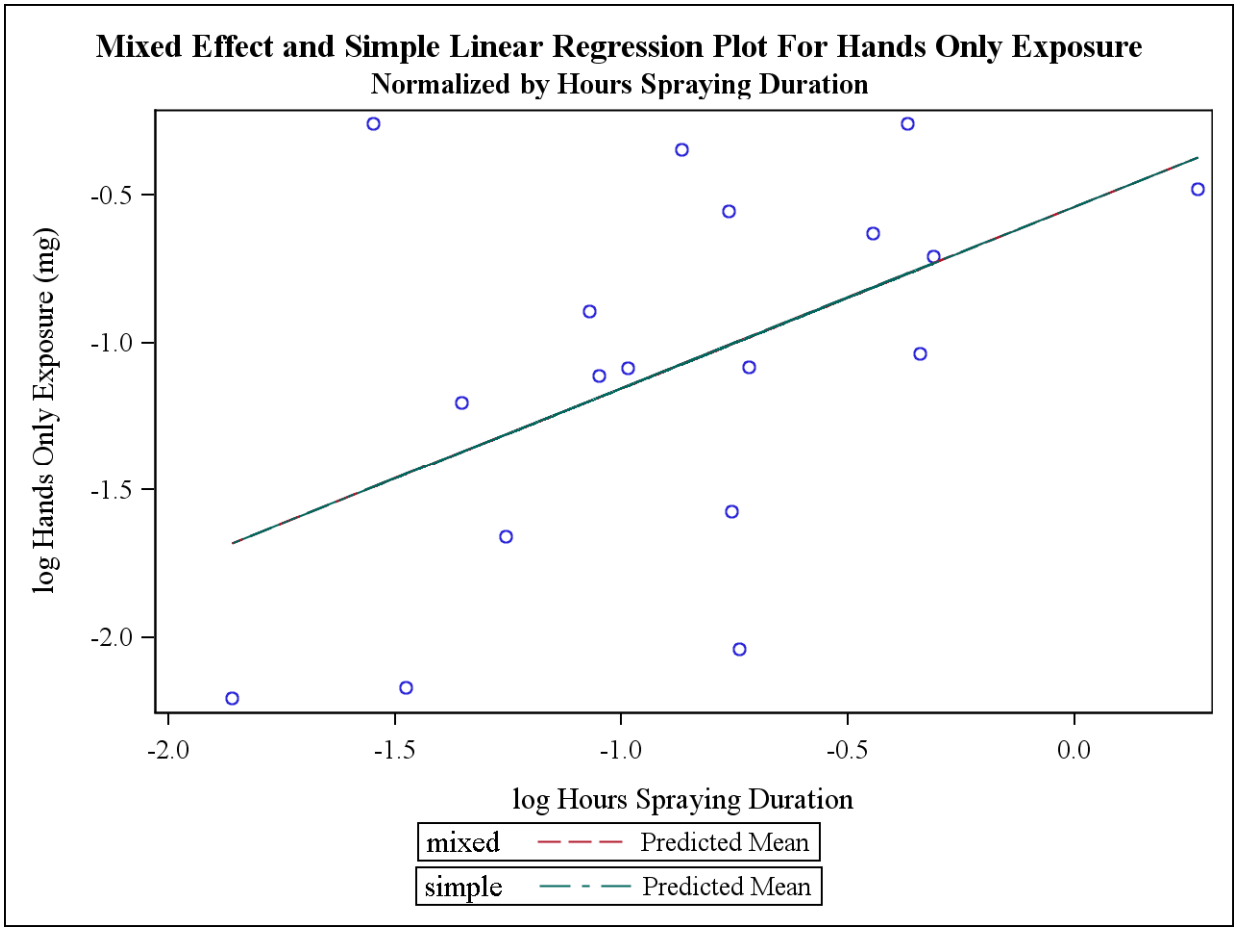
Mixed Effect and Simple Linear Regression Plot For Hands Only Exposure
Normalized by Hours Spraying Duration
log Hands Only Exposure (mg)
-0.5
-1.0
-1.5
-2.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 27b

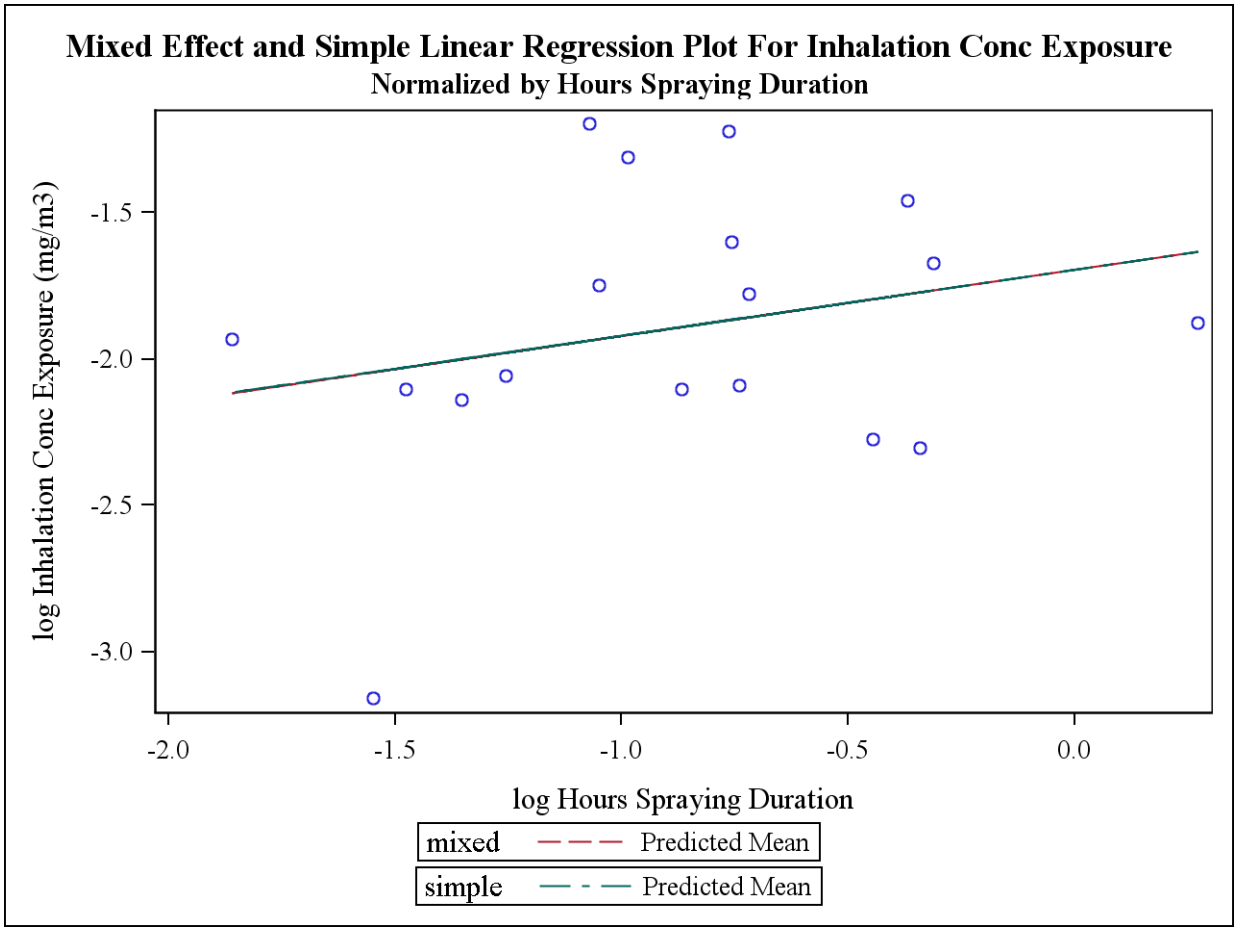
Mixed Effect and Simple Linear Regression Plot For Inhalation Conc Exposure
Normalized by Hours Spraying Duration
log Inhalation Conc Exposure (mg/m3)
-1.5
-2.0
-2.5
-3.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 28b

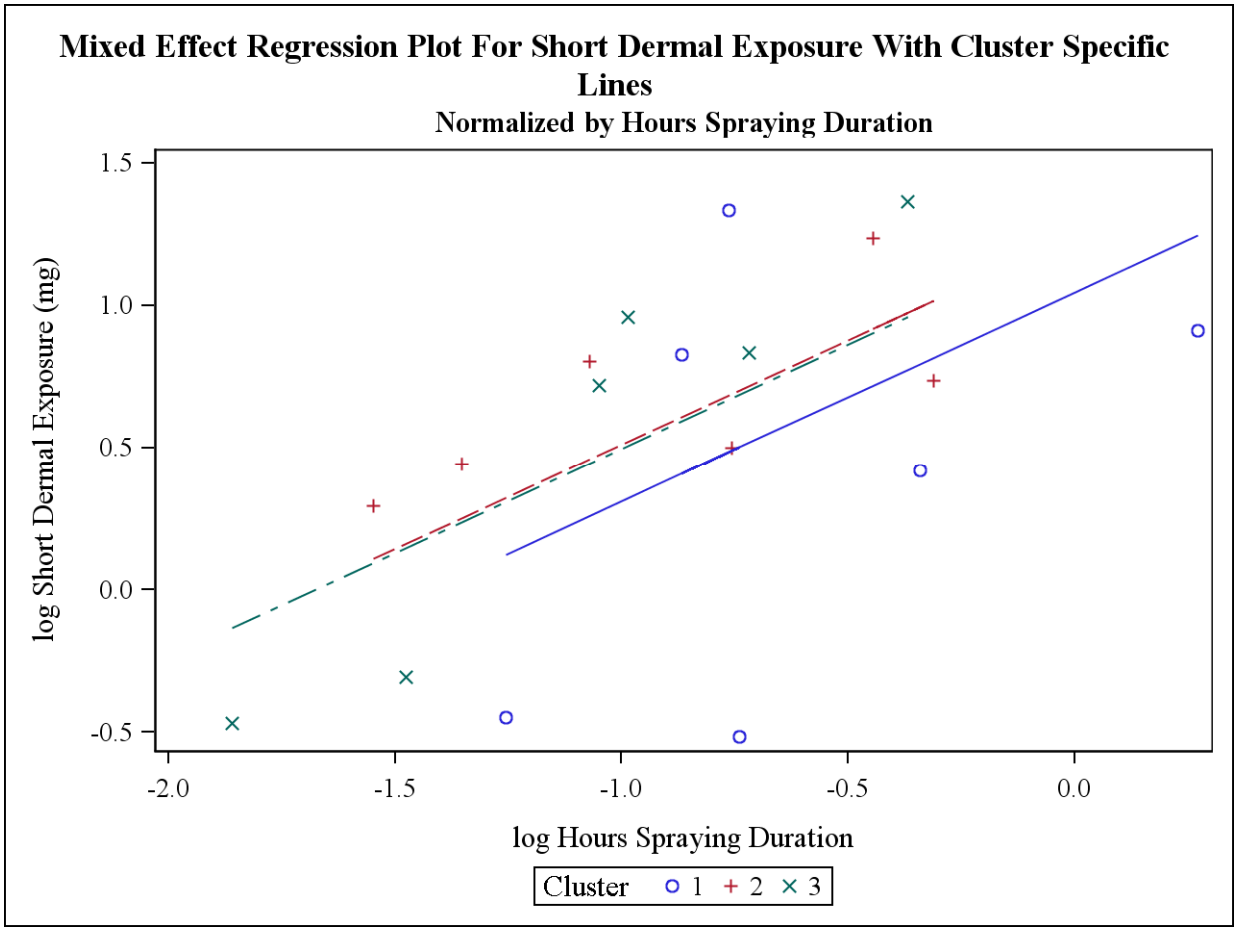
Mixed Effect Regression Plot For Short Dermal Exposure With Cluster Specific Lines
Normalized by Hours Spraying Duration
log Short Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-0.5
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
Cluster 1 2 3

Figure 29.1b

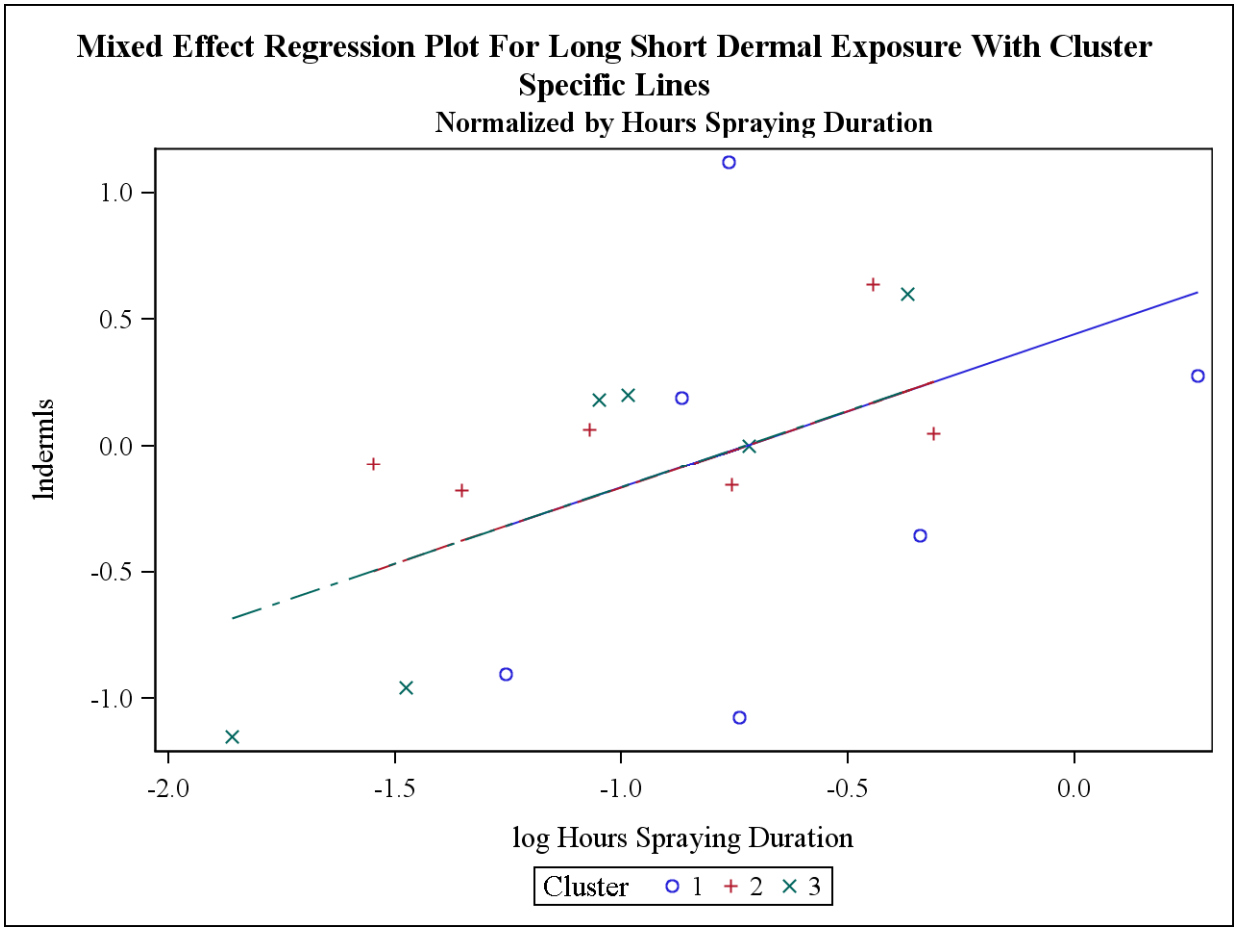
Mixed Effect Regression Plot For Long Short Dermal Exposure With Cluster Specific Lines
Normalized by Hours Spraying Duration
lndermls
1.0
0.5
0.0
-0.5
-1.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
Cluster 1 2 3

Figure 29.2b

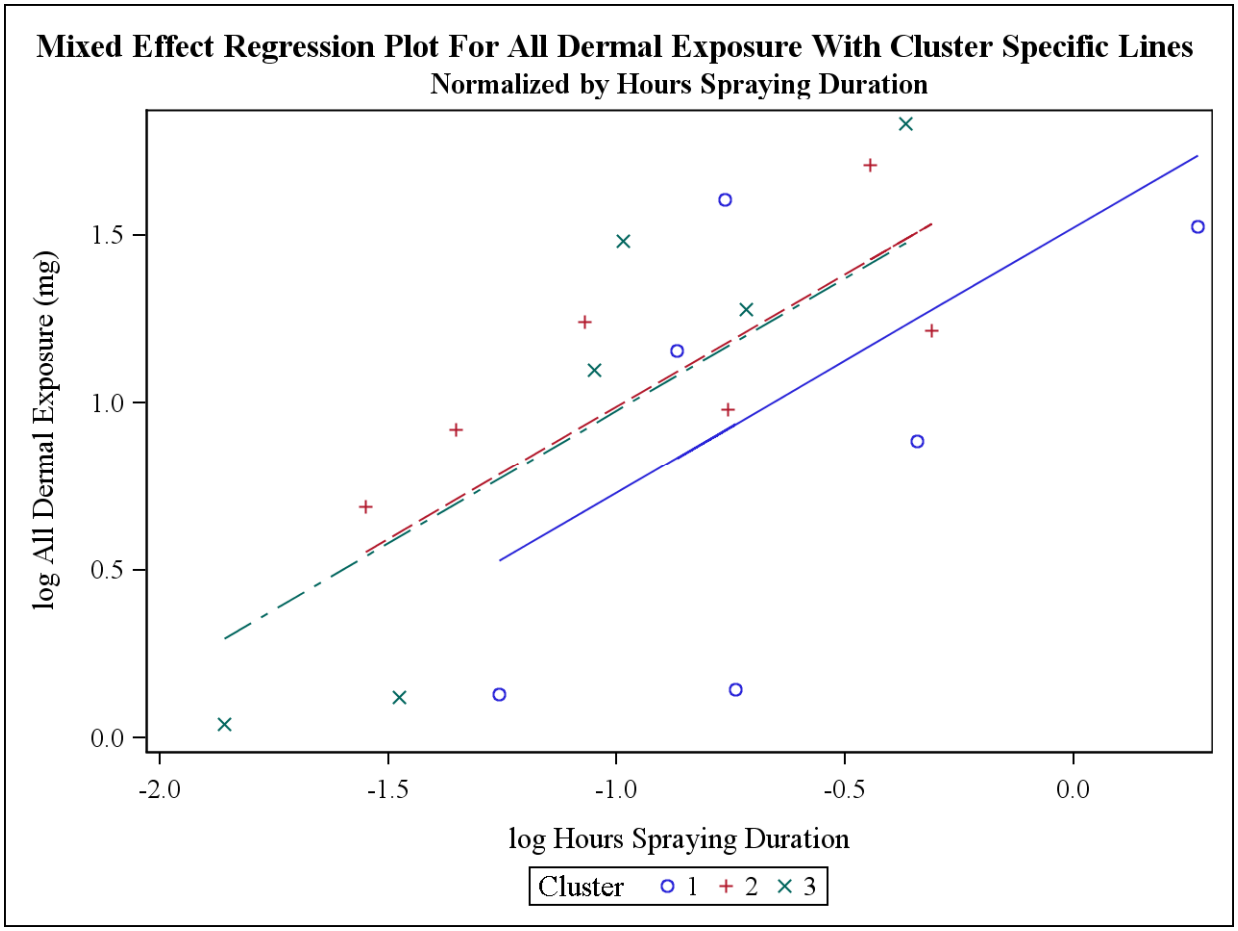
Mixed Effect Regression Plot For All Dermal Exposure With Cluster Specific Lines
Normalized by Hours Spraying Duration
log All Dermal Exposure (mg)
1.5
1.0
0.5
0.0
-2.0
-1.5
-1.0
-0.5
0.0
log Hours Spraying Duration
Cluster 1 2 3

Figure 29.3b

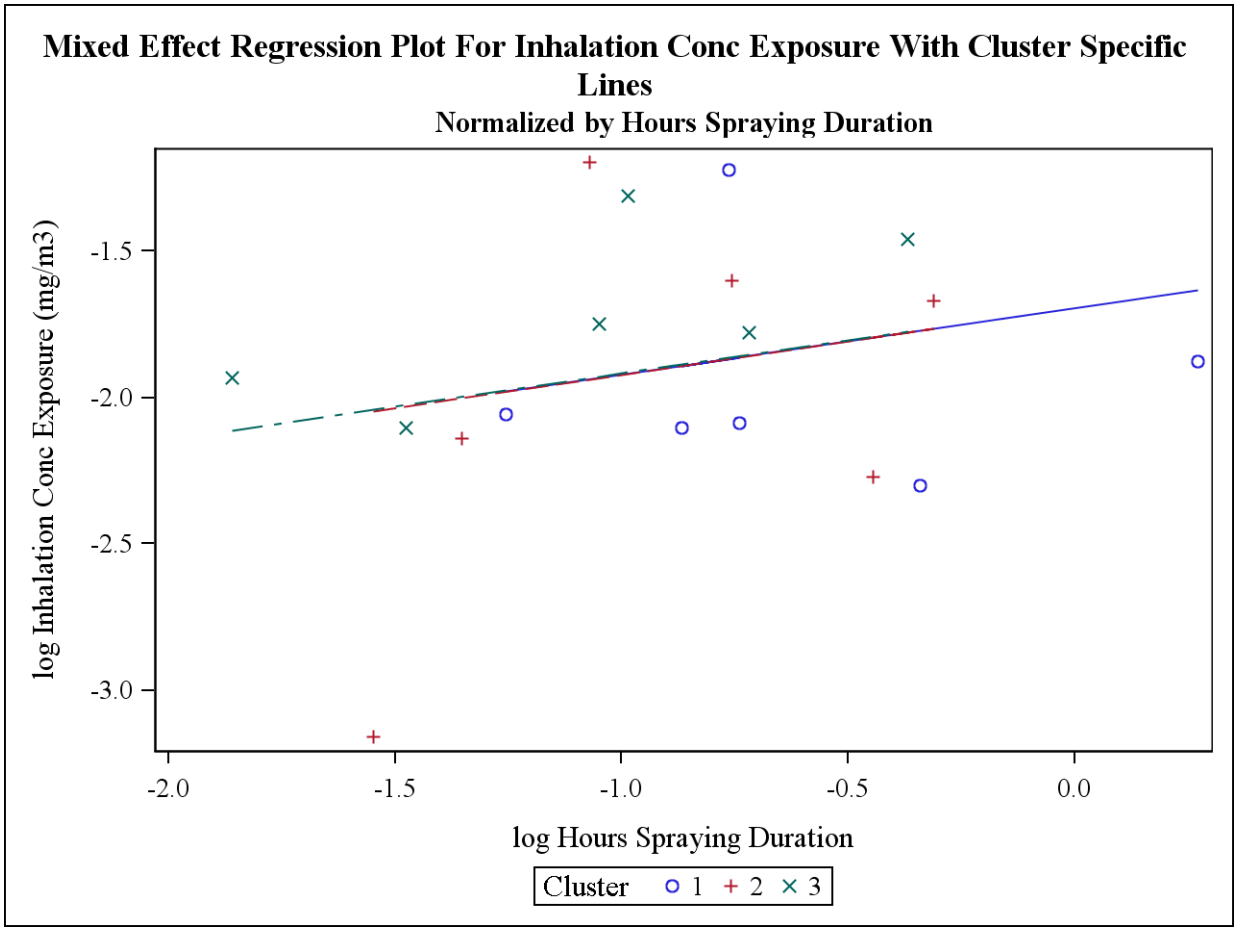

Figure 29.4b

Table 14b. Quadratic mixed models with 95% confidence intervals for the log exposure versus log spraying duration.

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Long Dermal	Intercept	-0.22	2.00	-1.68	1.24	1.85	0.00	2.93
Long Dermal	Slope	-0.23	13.00	-1.87	1.41	1.85	0.00	3.28
Long Dermal	Quad	-0.50	13.00	-1.41	0.41	1.85	0.00	1.82
Short Dermal	Intercept	0.99	11.16	0.32	1.66	1.67	0.11	1.34

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Short Dermal	Slope	0.03	13.35	-1.30	1.35	1.67	0.11	2.65
Short Dermal	Quad	-0.42	13.04	-1.15	0.30	1.67	0.11	1.45
Long Short Dermal	Intercept	0.25	2.00	-1.04	1.54	1.72	0.00	2.57
Long Short Dermal	Slope	-0.14	13.00	-1.58	1.31	1.72	0.00	2.88
Long Short Dermal	Quad	-0.44	13.00	-1.24	0.36	1.72	0.00	1.60
Hands Only	Intercept	-0.60	2.00	-1.99	0.79	1.79	0.00	2.78
Hands Only	Slope	0.39	13.00	-1.17	1.94	1.79	0.00	3.11
Hands Only	Quad	-0.14	13.00	-1.00	0.73	1.79	0.00	1.73
Inhalation	Intercept	-1.85	12.33	-2.45	-1.24	1.59	0.04	1.21
Inhalation	Slope	-0.40	13.61	-1.65	0.85	1.59	0.04	2.51
Inhalation	Quad	-0.38	13.21	-1.07	0.30	1.59	0.04	1.37
Dermal Repeated Measures	Slope	0.32	12.60	-1.03	1.68	NA	NA	2.71
Dermal Repeated Measures	Quad	-0.35	12.49	-1.09	0.40	NA	NA	1.49

Table 15b. Threshold values for the amount of active ingredient.

Exposure Route	**Clothing**	**Model**	**Slope**	**Threshold Level (hours)**
Dermal (mg)	Long pants and long sleeves	Mixed	0.61	0.40908
	Short pants and short sleeves	Mixed	0.73	0.40208
	Long pants and short sleeves	Mixed	0.61	0.40425
	Hands only	Mixed	0.61	0.40758
Inhalation (mg/m3)		Mixed	0.23	0.37555

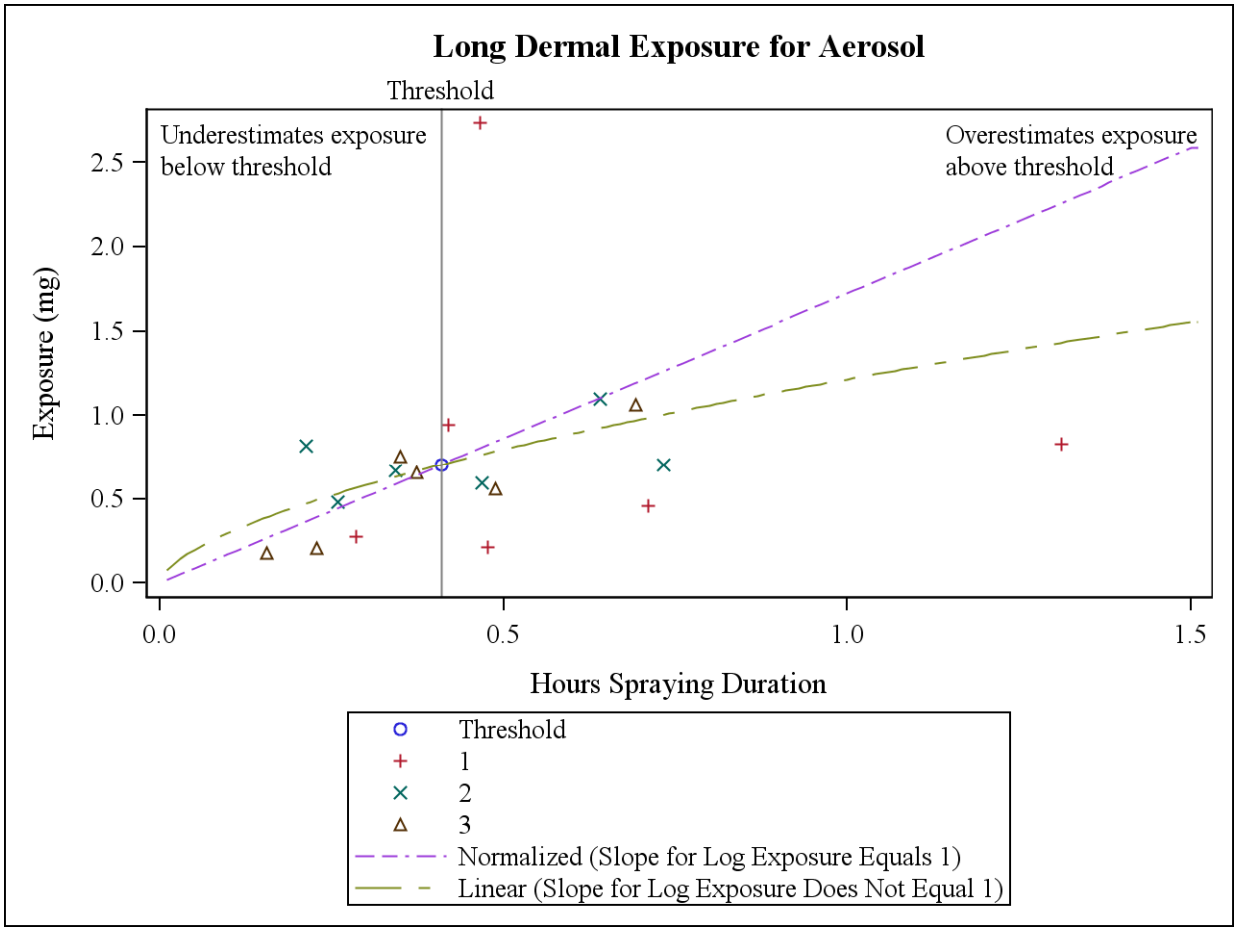
Long Dermal Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
2.5
2.0
1.5
1.0
0.5
0.0
0.0
0.5
1.0
1.5
Hours Spraying Duration
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 30b

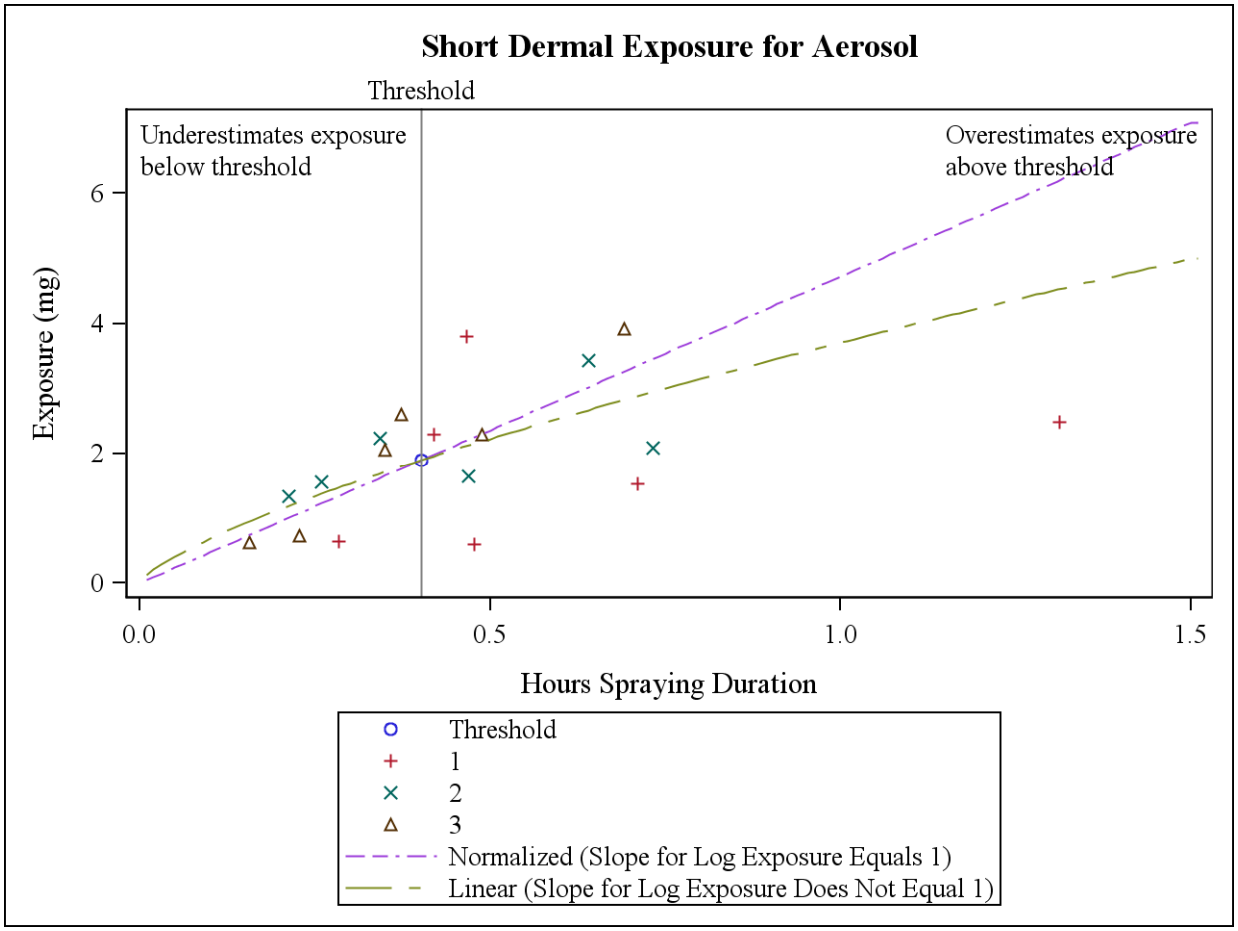
Short Dermal Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
2
4
6
0.0
0.5
1.0
1.5
Hours Spraying Duration
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 31b

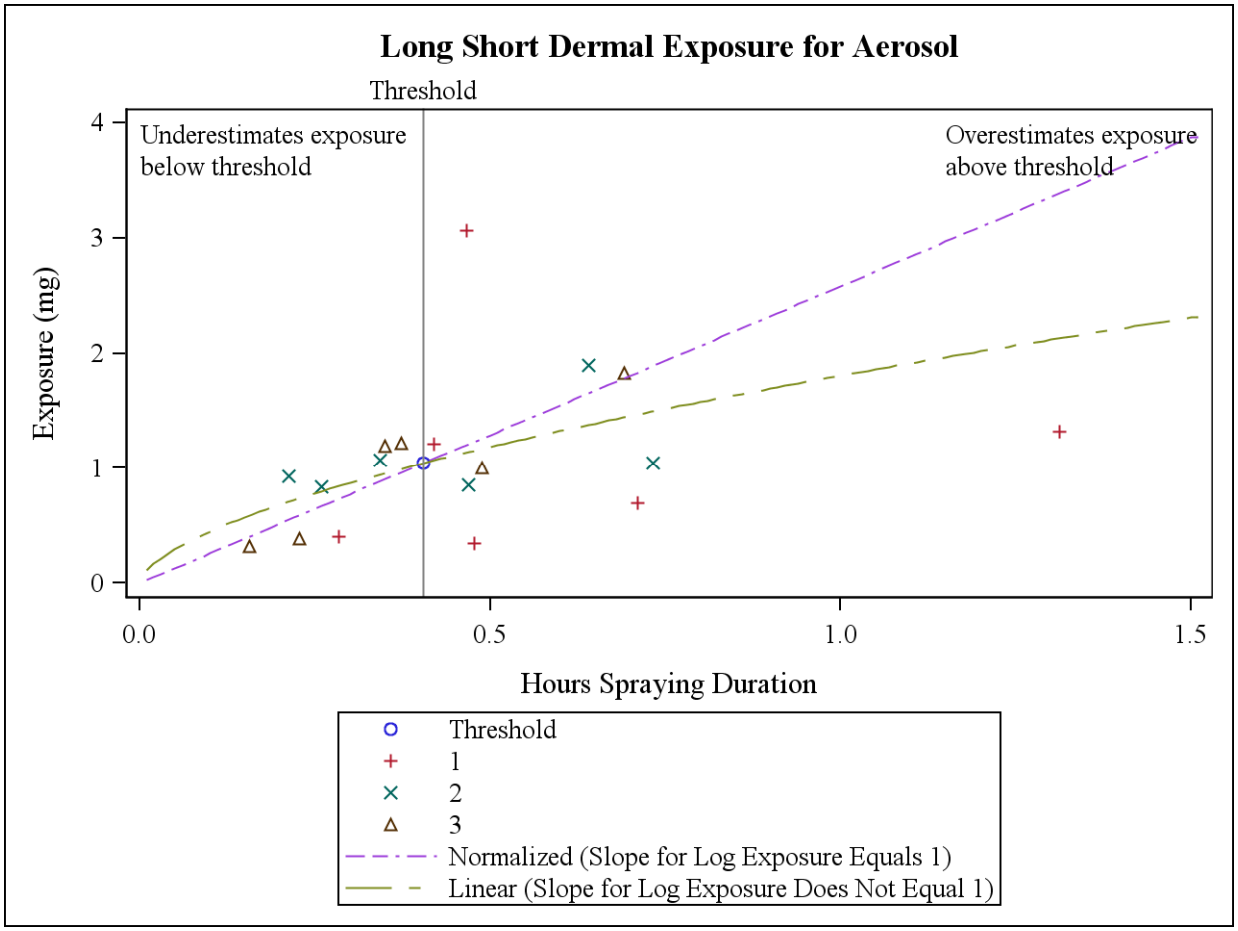
Long Short Dermal Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.0
0.5
1.0
1.5
Hours Spraying Duration
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 32b

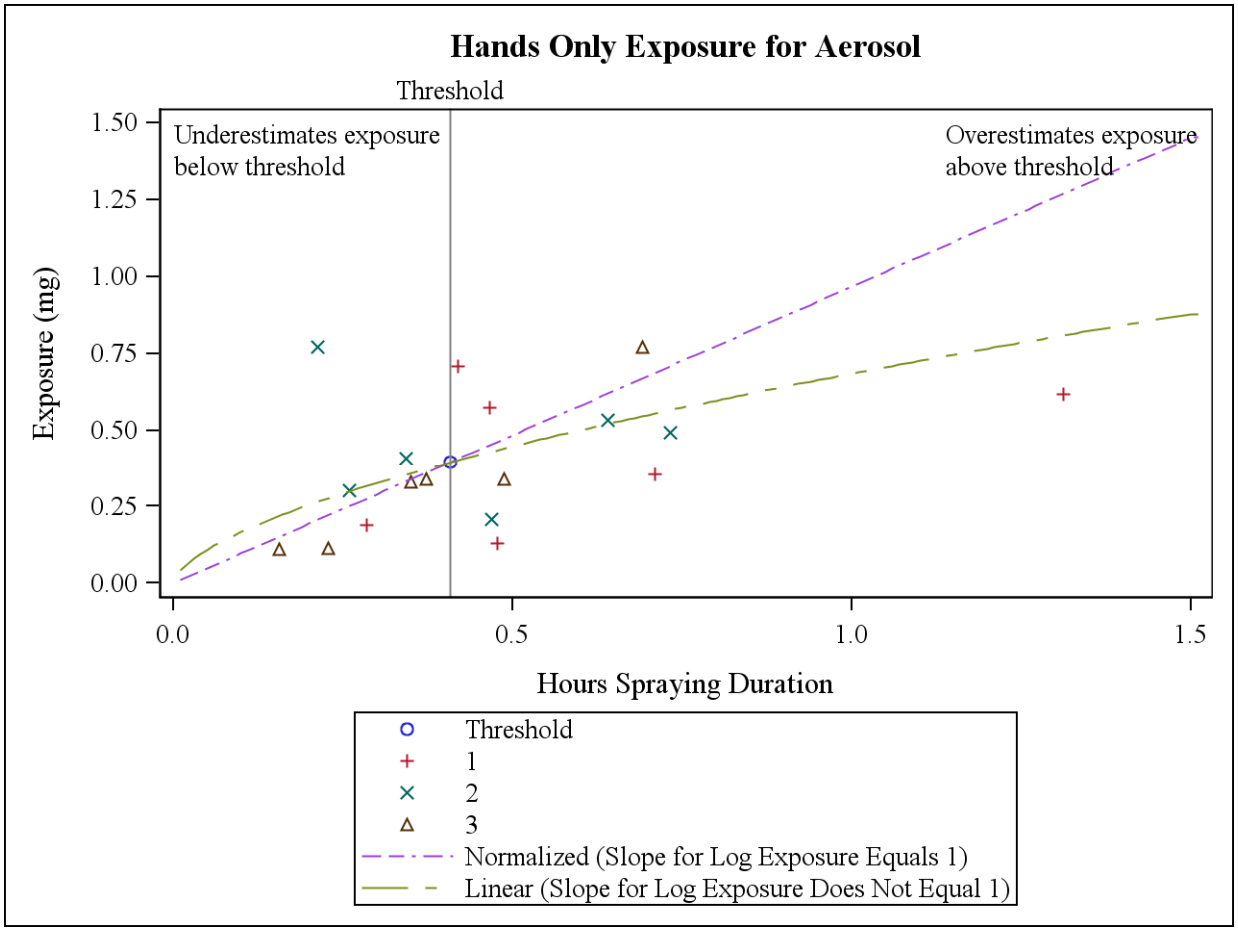
Hands Only Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0.0
0.5
1.0
1.5
Hours Spraying Duration
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 33b

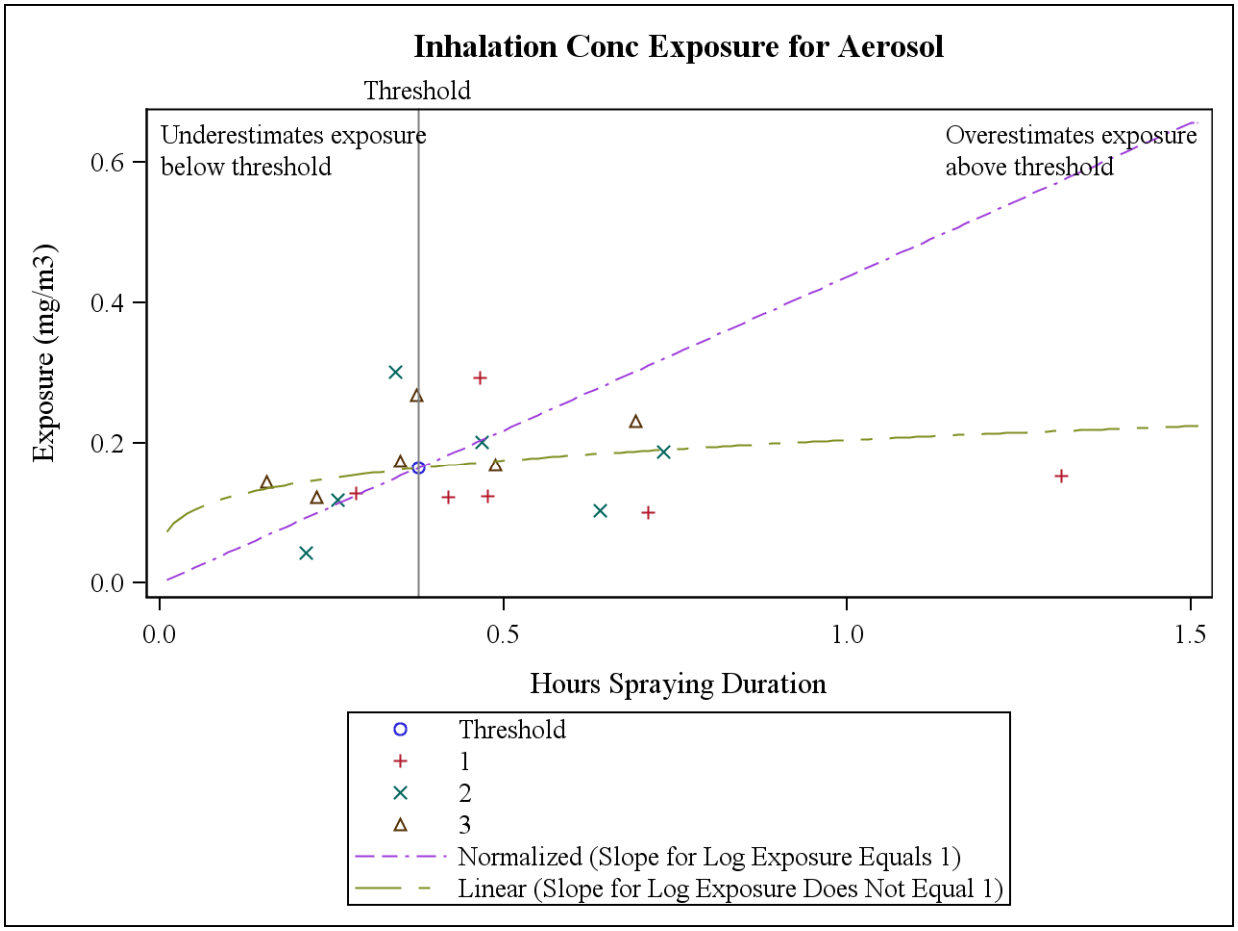
Inhalation Conc Exposure for Aerosol
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg/m3)
0.0
0.2
0.4
0.6
0.0
0.5
1.0
1.5
Hours Spraying Duration
Threshold
1
2
3
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 34b

Analyses of inhalation mass exposure per amount of active ingredient

Table and Figure Numbers are consistent with main text (add "c").

Inhalation mass exposure (mg) is estimated as air concentration (mg/m^3) × breathing rate (1 m^3/hour) × spraying duration (hours).

Table 2c. Summary statistics for normalized inhalation mass exposure.

Statistic	Normalized Inhalation Mass (mg/lb AI)	Normalized 100µm Inhalation Mass (mg/lb AI)	Normalized 10µm Inhalation Mass (mg/lb AI)	Normalized 2.5µm Inhalation Mass (mg/lb AI)
Arithmetic Mean	24.6	19.2	10.0	4.4
Arithmetic Standard Deviation	10.5	8.7	5.1	2.6
Geometric Mean	22.3	17.6	8.9	3.8
Geometric Standard Deviation	1.6	1.5	1.6	1.8
Min	6.7	8.7	3.9	1.0
5%	6.7	8.7	3.9	1.0
10%	13.3	9.5	4.8	1.9
25%	15.2	14.2	5.9	2.3
50%	23.9	16.0	8.5	3.9
75%	35.7	25.0	13.6	5.6
90%	39.1	32.0	20.7	8.8
95%	42.5	41.1	20.9	11.1
Max	42.5	41.1	20.9	11.1

Table 3c. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized inhalation mass exposure.

Exposure Route	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Inhalation mass (mg/lb AI)	25.1 (19.8, 32.0)	49.4 (34.8, 69.8)
100 μm inhalation mass (mg/lb AI)	19.4 (14.1, 26.9)	36.7 (24.0, 56.1)
10 μm inhalation mass (mg/lb AI)	10.1 (7.8, 13.3)	20.2 (13.8, 29.5)
2.5 μm inhalation mass (mg/lb AI)	4.5 (3.3, 6.2)	10.0 (6.5, 15.6)

Table 8c. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation mass exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.6	1.4	1.9	1.2	1.4	1.9	1.2
GSDm	1.6	1.4	1.9	1.2	1.4	1.9	1.2
ICC	0.0	0.0	0.4		0.0	0.5	
GMs	22.3	17.9	28.0	1.3	17.9	27.4	1.2
GMm	22.3	17.9	28.0	1.3	17.9	27.4	1.2
AMs	24.6	19.7	31.7	1.3	20.1	29.3	1.2
AMu	25.1	19.8	32.0	1.3	20.3	29.8	1.2
AMm	25.1	19.8	32.0	1.3	20.5	29.9	1.2
P95s	42.5	34.7	93.4	2.2	36.2	42.5	1.2
P95u	49.4	34.6	69.1	1.4	36.7	60.5	1.3
P95m	49.4	34.8	69.8	1.4	37.0	62.2	1.3

Table 9c. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 100μm inhalation mass exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.5	1.3	1.8	1.2	1.4	1.7	1.1
GSDm	1.6	1.3	1.9	1.2	1.4	1.8	1.1
ICC	0.2	0.0	0.7		0.0	0.7	
GMs	17.6	12.9	24.0	1.4	14.9	20.7	1.2
GMm	17.6	12.9	24.0	1.4	14.9	20.7	1.2
AMs	19.2	14.0	26.4	1.4	16.0	22.6	1.2
AMu	19.3	14.1	26.6	1.4	16.0	22.7	1.2
AMm	19.4	14.1	26.9	1.4	16.1	23.1	1.2
P95s	41.1	23.7	67.0	1.7	26.2	41.1	1.6
P95u	35.8	23.7	53.3	1.5	26.7	44.1	1.3
P95m	36.7	24.0	56.1	1.5	27.2	47.5	1.4

Table 10c. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 10μm inhalation mass exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.6	1.4	1.9	1.2	1.4	1.8	1.2
GSDm	1.6	1.4	2.0	1.2	1.4	1.9	1.1
ICC	0.0	0.0	0.5		0.0	0.7	
GMs	8.9	6.9	11.5	1.3	7.3	11.0	1.2
GMm	8.9	6.9	11.5	1.3	7.3	11.0	1.2
AMs	10.0	7.7	13.1	1.3	8.0	12.3	1.2
AMu	10.1	7.8	13.2	1.3	8.0	12.5	1.3
AMm	10.1	7.8	13.3	1.3	8.1	12.6	1.3
P95s	20.9	13.7	39.6	1.9	13.8	20.9	1.5
P95u	20.1	13.7	28.9	1.5	14.3	26.2	1.4
P95m	20.2	13.8	29.5	1.5	14.5	27.1	1.4

Table 11c. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized 2.5μm inhalation mass exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.8	1.5	2.2	1.2	1.5	2.1	1.2
GSDm	1.8	1.5	2.2	1.2	1.5	2.2	1.2
ICC	0.0	0.0	0.4		0.0	0.6	
GMs	3.8	2.9	5.1	1.3	3.0	4.9	1.3
GMm	3.8	2.9	5.1	1.3	3.0	4.9	1.3
AMs	4.4	3.3	6.1	1.4	3.4	5.6	1.3
AMu	4.5	3.3	6.2	1.4	3.5	5.7	1.3
AMm	4.5	3.3	6.2	1.4	3.5	5.8	1.3
P95s	11.1	6.4	22.1	2.0	5.7	11.1	1.9
P95u	10.0	6.4	15.3	1.6	6.8	13.7	1.5
P95m	10.0	6.5	15.6	1.6	6.9	14.5	1.5

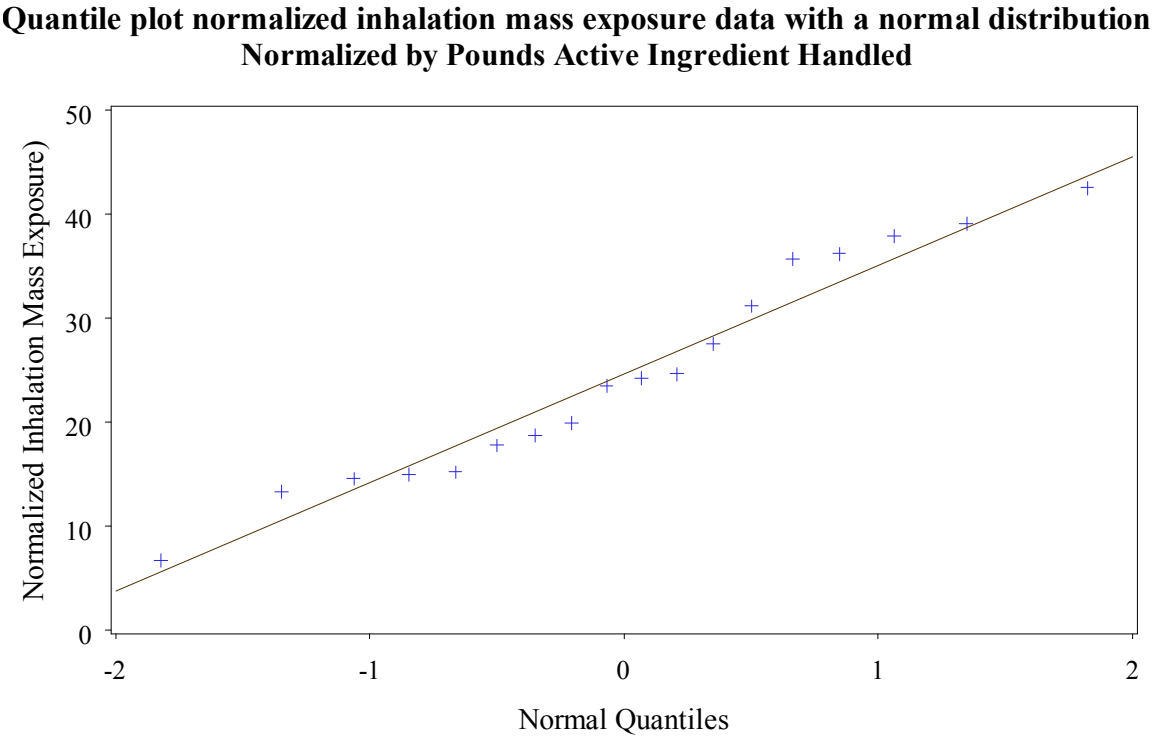

Figure 9c

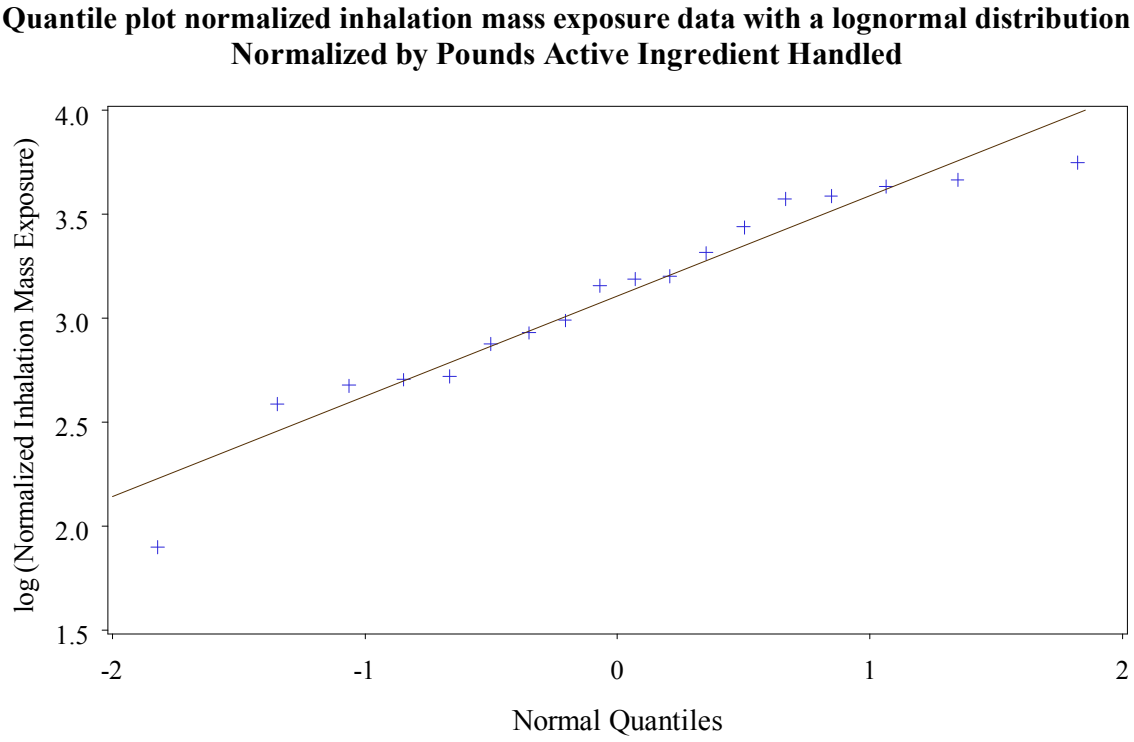
Quantile plot normalized inhalation mass exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Inhalation Mass Exposure)
4.0
3.5
3.0
2.5
2.0
1.5
-2
-1
0
1
2
Normal Quantiles

Figure 10c

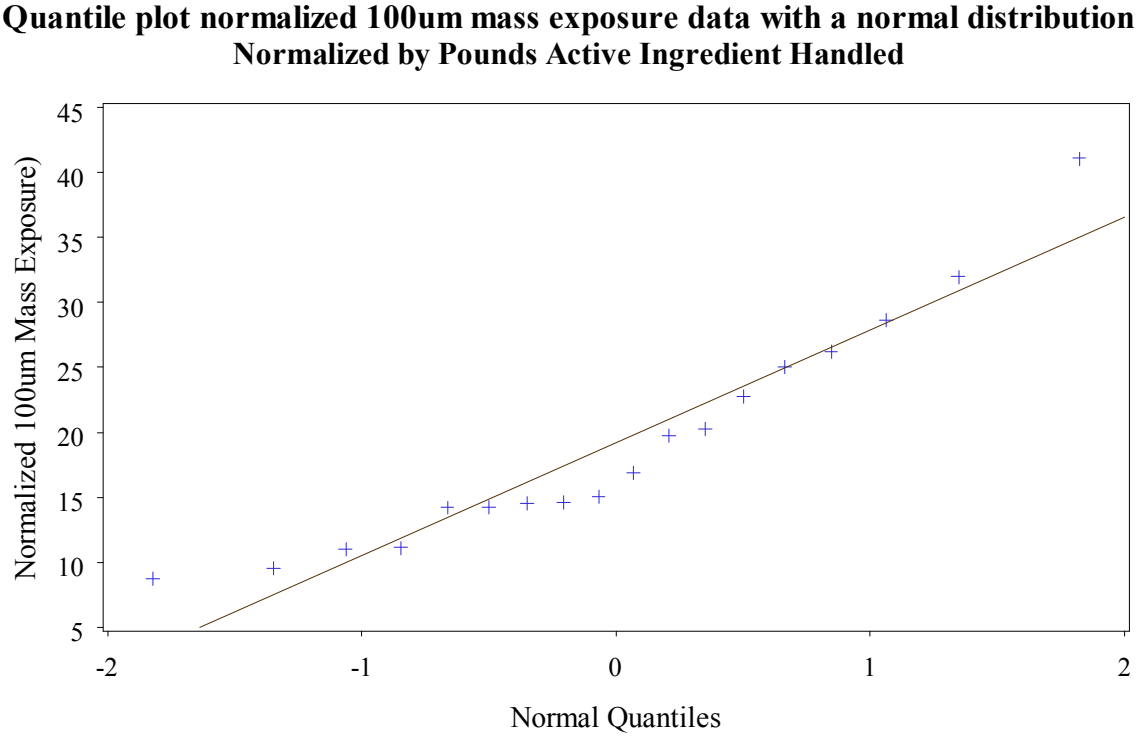
Quantile plot normalized 100um mass exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 100um Mass Exposure)
45
40
35
30
25
20
15
10
5
-2
-1
0
1
2
Normal Quantiles

Figure 11c

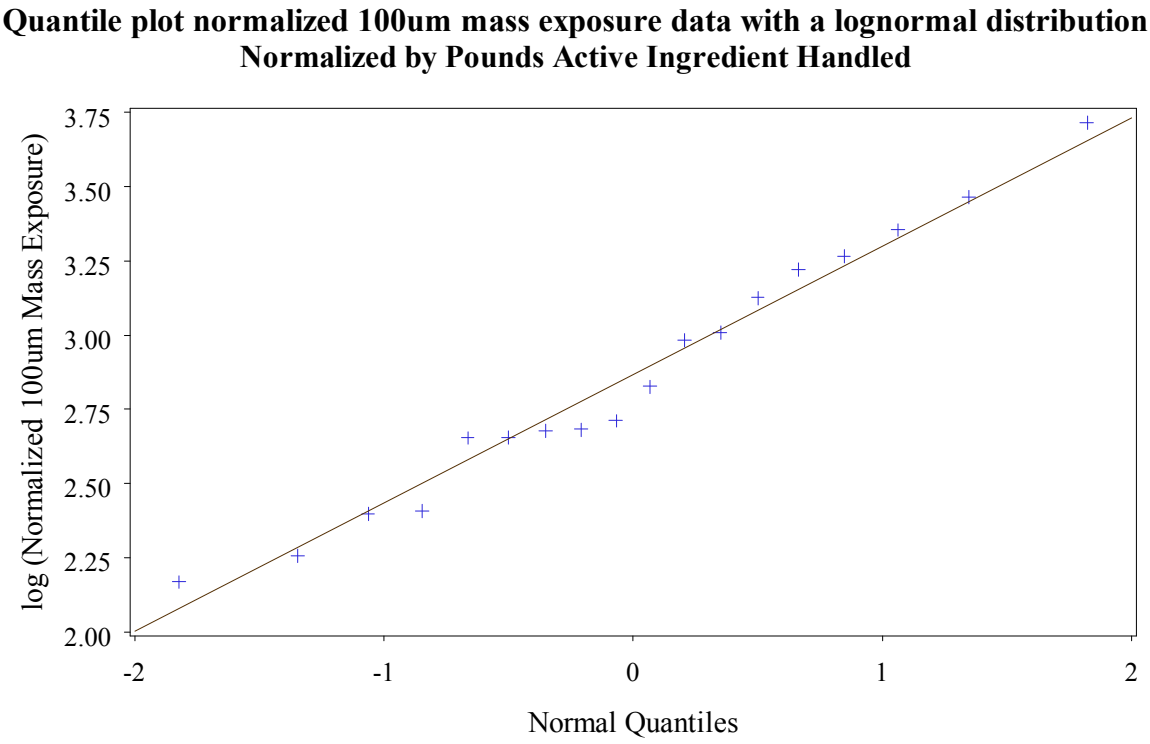
Quantile plot normalized 100um mass exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 100um Mass Exposure)
3.75
3.50
3.25
3.00
2.75
2.50
2.25
2.00
-2
-1
0
1
2
Normal Quantiles

Figure 12c

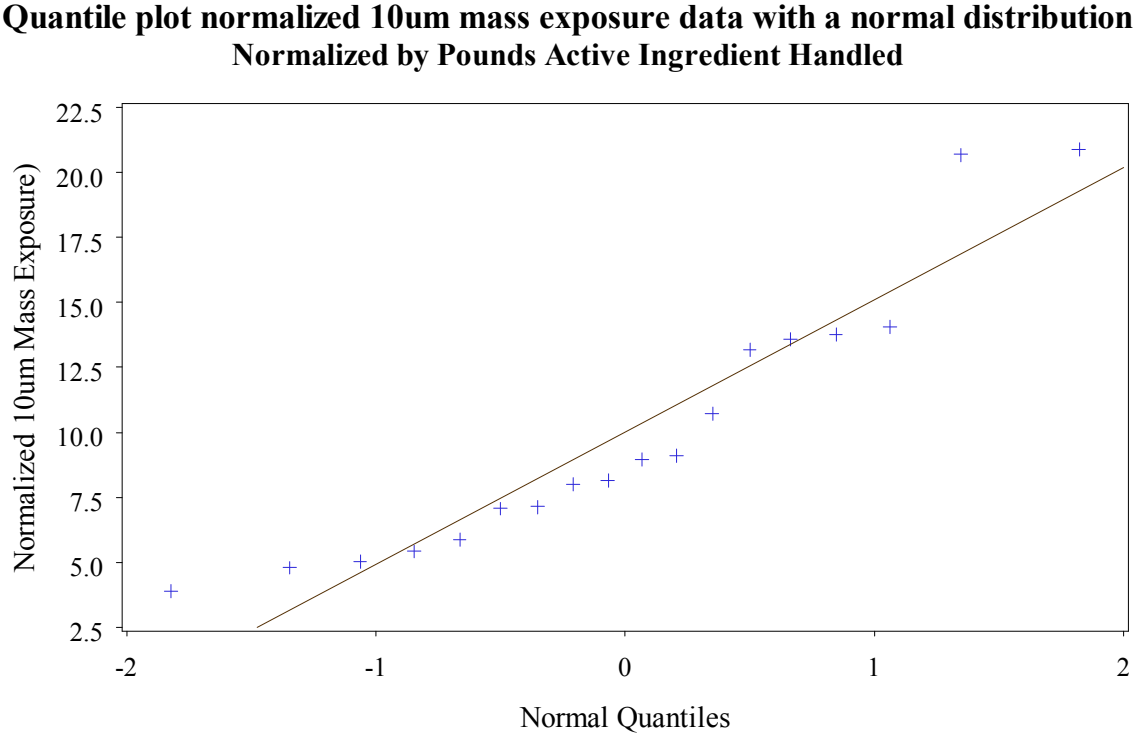
Quantile plot normalized 10um mass exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 10um Mass Exposure)
22.5
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
-2
-1
0
1
2
Normal Quantiles

Figure 13c

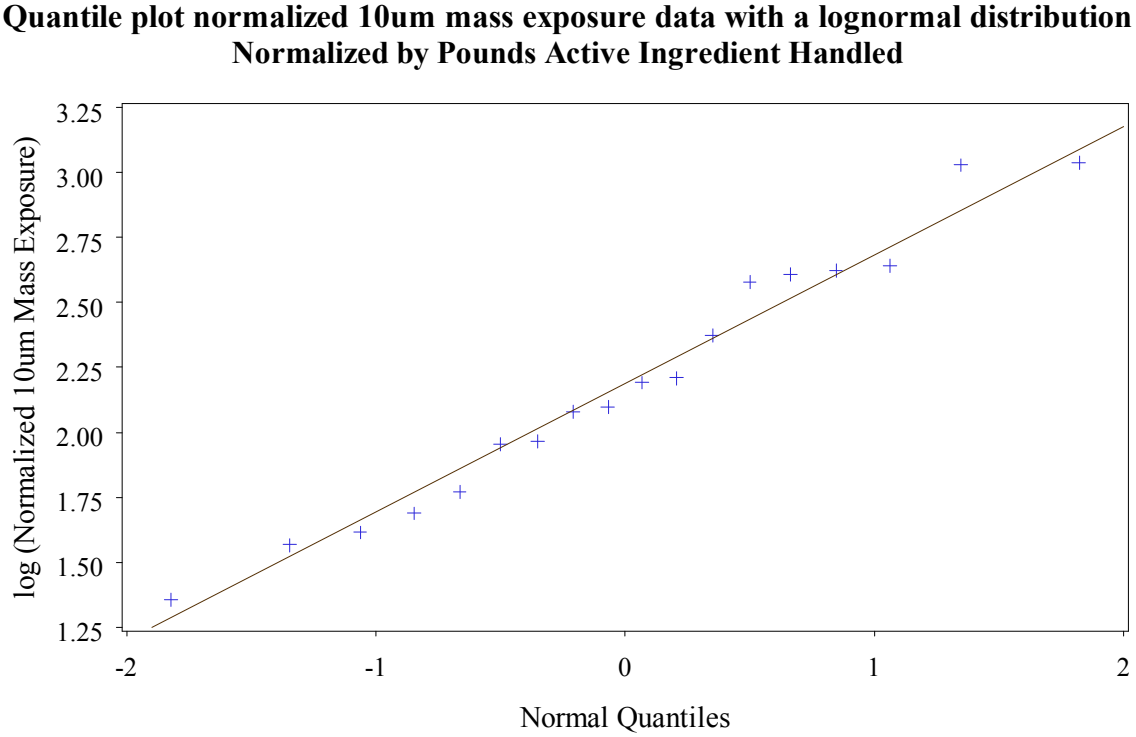
Quantile plot normalized 10um mass exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 10um Mass Exposure)
3.25
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
-2
-1
0
1
2
Normal Quantiles

Figure 14c

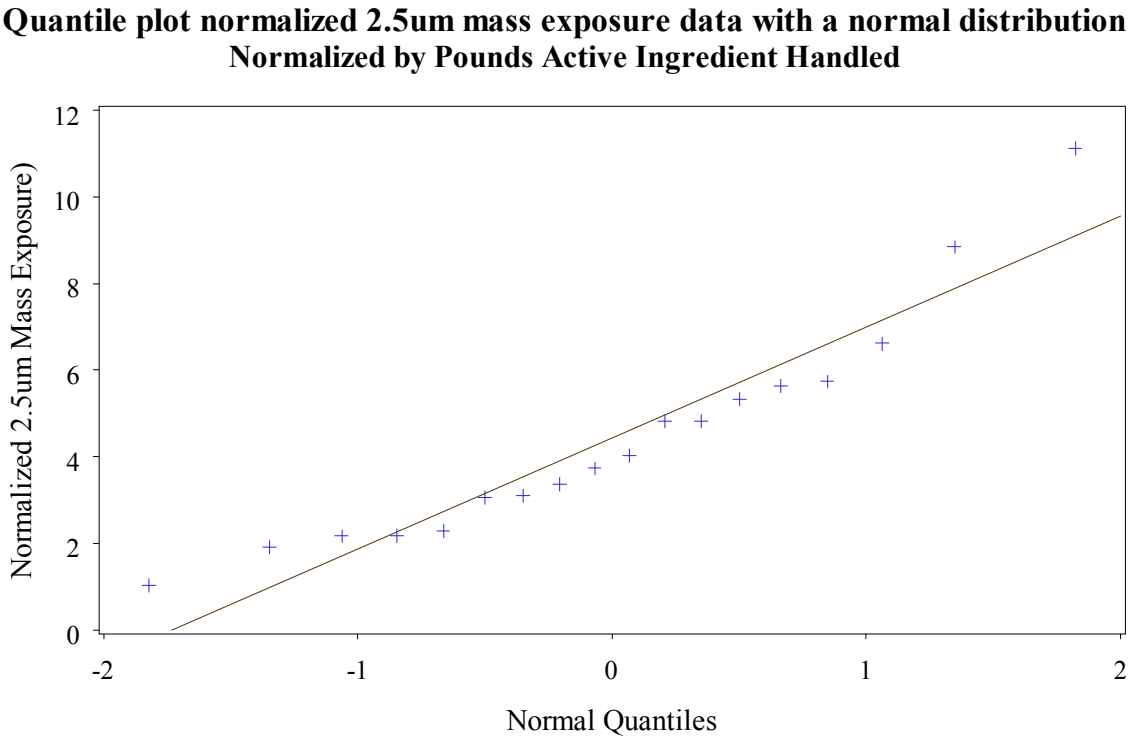
Quantile plot normalized 2.5um mass exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized 2.5um Mass Exposure)
12
10
8
6
4
2
0
-2
-1
0
1
2
Normal Quantiles

Figure 15c

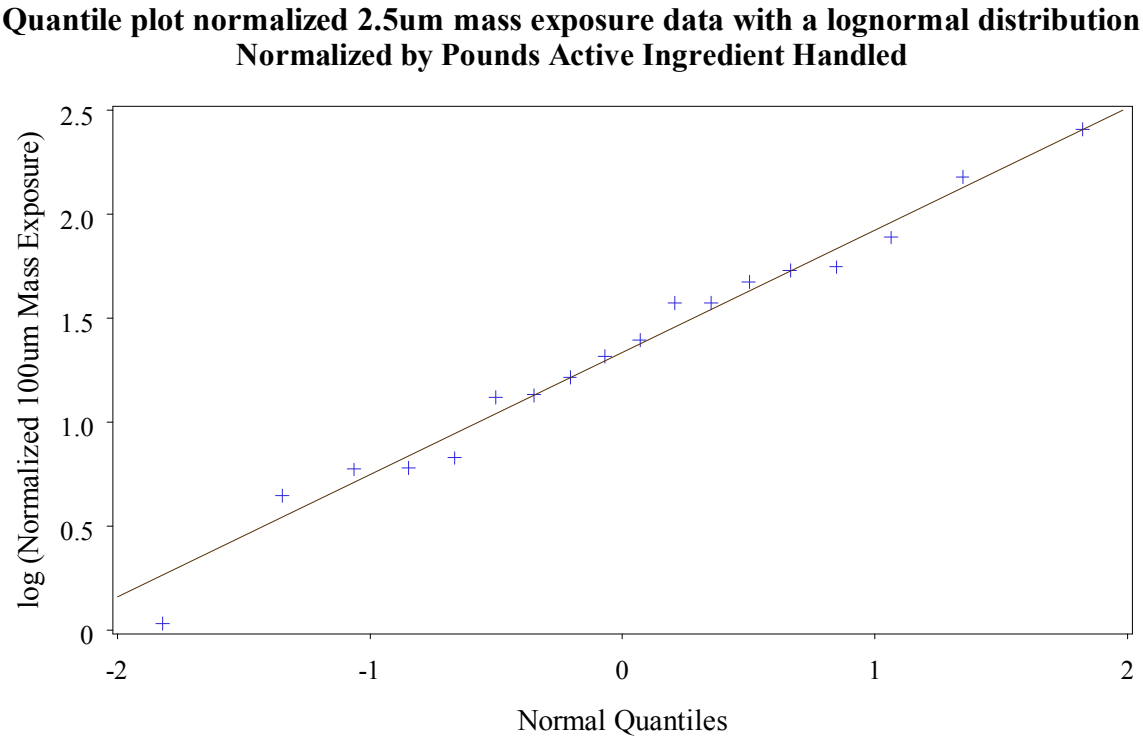
Quantile plot normalized 2.5um mass exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized 100um Mass Exposure)
2.5
2.0
1.5
1.0
0.5
0
-2
-1
0
1
2
Normal Quantiles

Figure 16c

Table 13c. 95 percent confidence intervals for the slope of log inhalation exposure mass versus log pounds active ingredient handled.

Exposure Route	Model	Estimate	Lower	Upper	Confidence Interval Width
Inhalation mass (mg)	Mixed	1.55	1.02	2.08	1.05
	Simple Linear	1.55	1.03	2.07	1.04

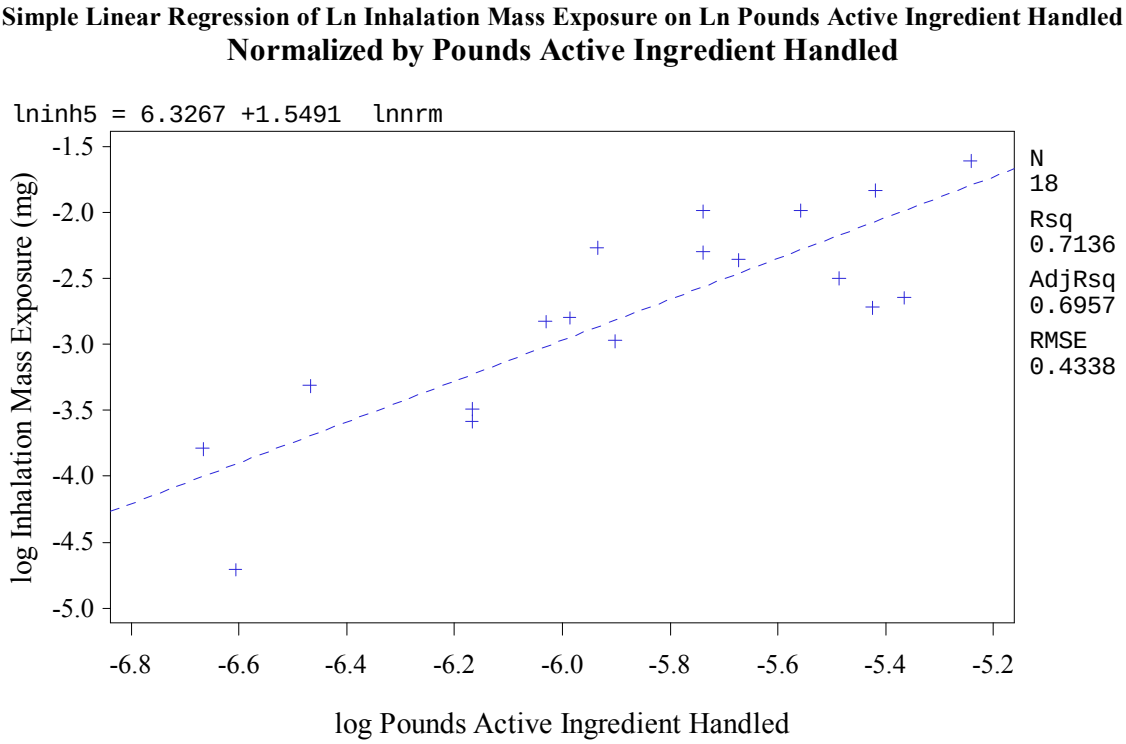

Figure 22c

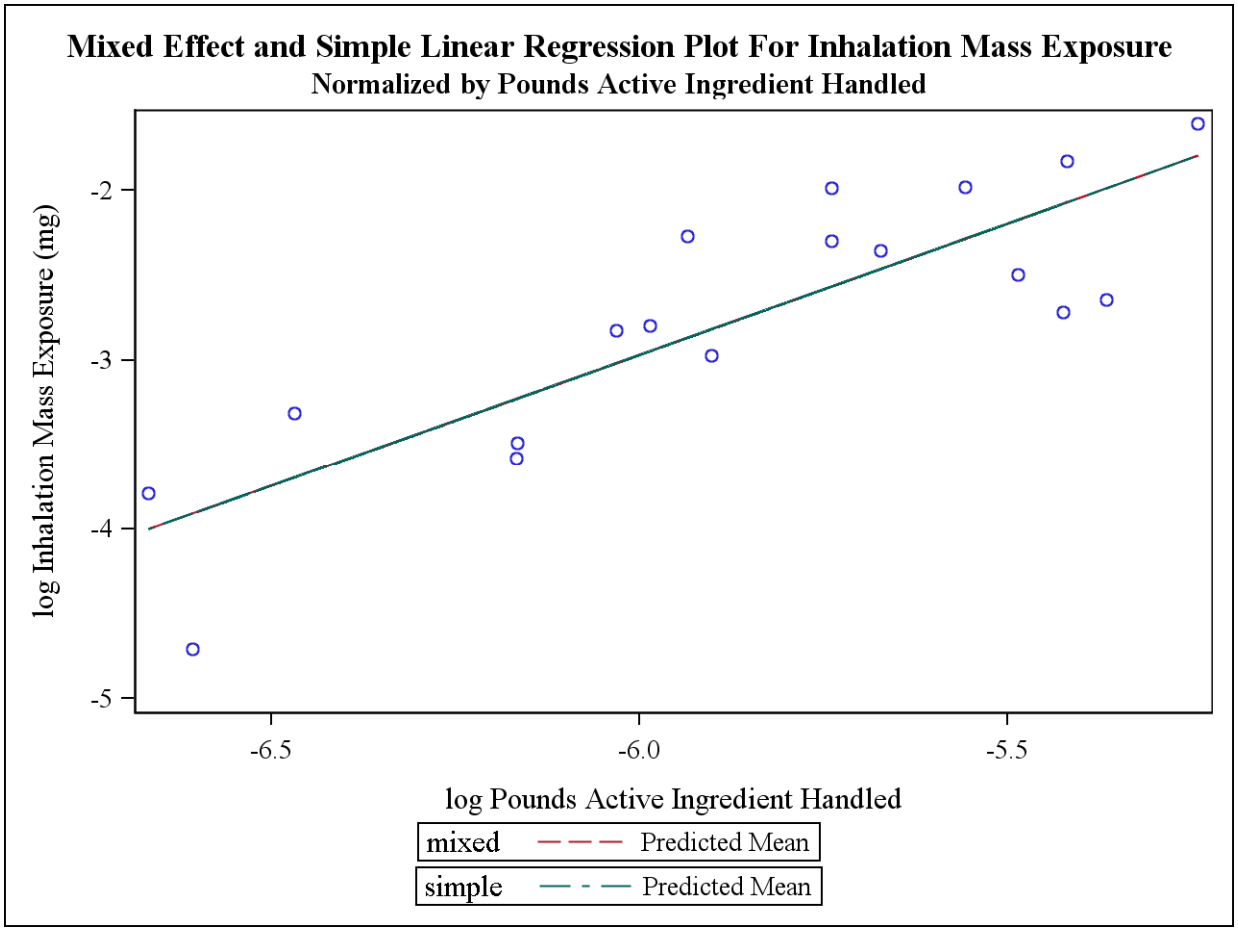

Figure 28c

Table 14c. Quadratic mixed models with 95% confidence intervals for the log inhalation mass exposure versus log pounds active ingredient handled.

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Inhalation mass	Intercept	-18.51	2.00	-106.93	69.92	1.53	0.00	176.85
Inhalation mass	Slope	-6.83	13.00	-21.79	8.13	1.53	0.00	29.92
Inhalation mass	Quad	-0.70	13.00	-1.96	0.55	1.53	0.00	2.51

Table 15c. Threshold values for the amount of active ingredient.

Exposure Route	Model	Slope	Threshold Level (lb active ingredient)
Inhalation mass (mg)	Mixed	1.55	0.00295*

*For this case, slope > 1 and so the normalized exposure mixed model under-predicts exposure for pounds of active ingredient above the threshold.

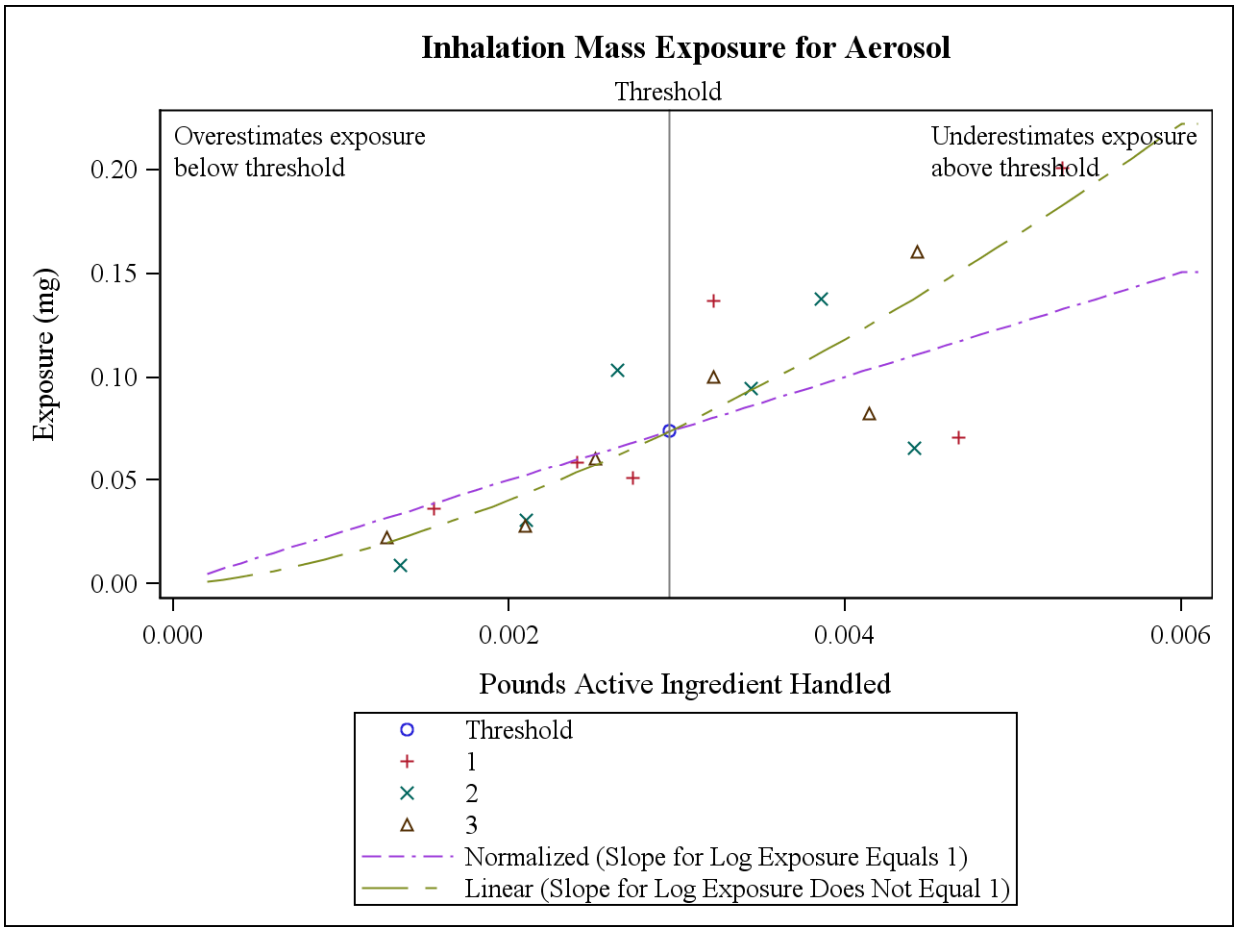

Figure 34c